Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

List of Subjects in 9 CFR Part 94

Animal diseases, Imports, Livestock, Meat and meat products, Milk, Poultry and poultry products, Reporting and recordkeeping requirements.

Accordingly, 9 CFR part 94 would be amended as follows:

PART 94—RINDERPEST, FOOT-AND-MOUTH DISEASE, FOWL PEST (FOWL PLAGUE), EXOTIC NEWCASTLE DISEASE, AFRICAN SWINE FEVER, HOG CHOLERA, AND BOVINE SPONGIFORM ENCEPHALOPATHY: PROHIBITED AND RESTRICTED IMPORTATIONS

1. The authority citation for part 94 would continue to read as follows:

Authority: 7 U.S.C. 147a, 150ee, 161, 162, and 450; 19 U.S.C. 1306; 21 U.S.C. 111, 114a, 134a, 134b, 134c, 134f, 136, and 136a; 31 U.S.C. 9701; 42 U.S.C. 4331 and 4332; 7 CFR 2.22, 2.80, and 371.2(d).

2. Section 94.1 would be amended as follows:

a. In paragraph (a)(1), the words "or (a)(3)" would be added immediately after the words "paragraph (a)(2)".

b. In paragraph (a)(2), the word "Luxembourg," would be added immediately after the word "Japan," and the word "Portugal," would be added immediately after the word "Poland,";

c. A new paragraph (a)(3) would be added to read as set forth below.

d. In the introductory text of paragraph (c), the words "paragraph (a) of" would be removed and the words "paragraph (a)(2) of" would be added in their place.

§ 94.1 Regions where rinderpest or foot-and-mouth disease exists; importations prohibited.

(a) * * *

(3) The following regions are declared to be free of rinderpest: Greece.

* * * * * *

§ 94.3 [Amended]

3. Section 94.3 would be amended by adding the words "where rinderpest or foot-and-mouth disease exists, as" immediately before the word "designated".

§ 94.4 [Amended]

4. In § 94.4(a), the introductory text of the paragraph would be amended by adding the words "where rinderpest or foot-and-mouth disease exists, as" immediately before the word "designated".

§ 94.6 [Amended]

5. In § 94.6, paragraph (a)(2) would be amended by adding the words "France, Greece," immediately after the word "Finland,"; by adding the word "Luxembourg," immediately after the word "Iceland,"; and by adding the word "Spain," immediately after the words "Republic of Ireland,".

§ 94.8 [Amended]

6. In § 94.8, the introductory text of the section would be amended by removing the words "Malta, and Portugal" and adding in their place the words "and Malta".

§ 94.11 [Amended]

7. In § 94.11, paragraph (a), the first sentence would be amended by adding the word "Luxembourg," immediately after the word "Japan,"; by adding the word "Portugal," immediately after the word "Poland,"; and by removing the reference "§ 94.1" and adding the reference "§ 94.1(a)(2)" in its place.

§ 94.12 [Amended]

8. In § 94.12, paragraph (a) would be amended by adding the word "Belgium," immediately after the words "The Bahamas,"; by adding the word "France," immediately after the word "Finland,"; and by adding the word "Portugal," immediately after the word "Panama,".

§ 94.13 [Amended]

9. In § 94.13, the introductory text of the section would be amended by adding the word "Belgium," immediately after the words "The Bahamas,"; by adding the word "France," immediately after the word "Denmark,"; and by adding the word "Portugal," immediately after the words "North... Irel...d,".

Done in Washington, DC, this 12th day of November 1997.

Terry L. Medley,

Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 97–30105 Filed 11–13–97; 8:45 am]

BILLING CODE 3410–34–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 77N–094W]

RIN 0910–AA01

Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish alcohol warnings for all over-the-counter (OTC) drug products containing internal analgesic/antipyretic active ingredients labeled for adult use. The proposed warning statements advise consumers who have a history of heavy alcohol use or abuse to consult a physician for advice about the use of OTC internal analgesic/antipyretic drug products. A warning would be required for all OTC internal analgesic/antipyretic drug products marketed under an OTC drug monograph or an approved new drug application (NDA). FDA is issuing this notice of proposed rulemaking after considering the reports and recommendations of its Nonprescription Drugs Advisory Committee (NDAC) and Arthritis Drugs Advisory Committee (ADAC), public comments on the proposed rule for OTC internal analgesic, antipyretic, and antirheumatic drug products, and other available information.

DATES: Written comments by January 28, 1998. Written comments on the agency's economic impact determination by January 28, 1998. The agency is proposing that any final rule based on this proposal be effective 6 months after the date of its publication in the Federal Register.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Debbie L. Lumpkins, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2241.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of July 8, 1977 (42 FR 35346), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, together with the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (the Panel), which was the panel responsible for evaluating data on the active ingredients in these drug products. In that notice, the Panel discussed the effects of alcohol ingestion on the safe use of OTC internal analgesic, antipyretic, and antirheumatic drug products containing aspirin and acetaminophen (42 FR 35346 at 35395).

Based on the data evaluated, the Panel found evidence of a possible synergism between alcohol and aspirin's ability to cause gastrointestinal (GI) bleeding (42 FR 35346 at 35395). The Panel stated that the data supported the hypothesis that aspirin may enhance or potentiate bleeding from GI lesions, even though aspirin alone may not initiate the lesion. However, the Panel stopped short of recommending a warning concerning the use of aspirin with alcohol.

The Panel did not receive data on the effect of alcohol use with other salicylates. However, based on its evaluation of the available data, the Panel concluded that carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate all have safety profiles similar to aspirin and should bear similar labeling (42 FR 35346 at 35417 through 35422).

In evaluating the safety of acetaminophen (42 FR 35346 at 35413 to 35415), the Panel considered data on the metabolism of acetaminophen in the presence of various types of liver disease, including alcoholic liver cirrhosis. The Panel determined that the decreased metabolism of acetaminophen by the usual principal mechanisms (glucuronidation and sulfation) observed in some people with chronic liver disease could potentially increase the toxicity of acetaminophen by increasing the relative fraction metabolized through the other pathway(s) leading to the toxic metabolite. The Panel found that the evidence suggested that the overall elimination of acetaminophen by conjugation is decreased in alcohol abusers and is similar to that observed in cases of decreased liver function. The Panel suggested, however, that this decreased conjugation and the increased susceptibility of chronic alcohol abusers to the hepatotoxicity of acetaminophen was not necessarily due to liver cirrhosis but resulted from the induction of microsomal enzymes by the chronic use of alcohol. However, the Panel did not recommend a warning concerning the use of normal doses of acetaminophen by individuals with a history of liver disease or chronic alcohol abuse. The Panel's recommended label warning on liver damage referred only to the well-documented injury that can occur with overdose. The Panel recommended the following warning: "Do not exceed recommended dosage because severe liver damage may occur."

In the Federal Register of November 16, 1988 (53 FR 46204), the agency published a proposed rule (tentative final monograph) for OTC internal analgesic, antipyretic, and antirheumatic drug products. In the preamble to the proposed rule, the agency responded to a number of comments concerning the Panel's recommended liver warning for acetaminophen and the need for a warning on the increased risk of liver toxicity when acetaminophen is taken with substances or drugs that induce microsomal enzyme activity, i.e., alcohol, barbiturates, or prescription drugs for epilepsy (53 FR 46204 at 46213 through 46218). The agency found that the available data did not provide a sufficient basis to require such a warning.

The agency also received a number of comments opposed to warnings that cite organs of the body as possible cites for damage from acute overdoses of internal analgesic/antipyretic drug products. The agency agreed with the comments and determined that warnings for acetaminophen need not specify the toxic effects on particular organs of the body that can be caused by acute overdose of a drug, as in a suicide attempt. However, the agency further stated (53 FR 46204 at 46213):

> * * * the warnings should include specific information on the known side effects or adverse reactions that may occur from use of the drug according to labeled directions, as well as potential dangers that may occur if the labeled directions are exceeded.
>
> The agency concludes that when medical evidence shows that toxicity is associated with the use of an OTC drug, either within its recommended dosage or when used beyond its recommended time limit or dosage (except for acute overdose), it is appropriate to warn consumers of the potential toxicity. In some cases it may be necessary to include organ-specific warnings as well as general labeling statements.

The agency received no comments concerning the Panel's comments about a possible synergism between alcohol and aspirin's ability to cause GI bleeding or the lack of a reference to such effect in labeling.

II. Summary of the Comments Received

In response to the proposed rule, the agency received comments concerning the need for an alcohol warning for acetaminophen. One comment recommended that the labeling of OTC drug products containing acetaminophen include the following warning: "Do not drink alcoholic beverages while taking acetaminophen. To do so may increase the chance of liver damage, especially if you drink large amounts of alcoholic beverages regularly." Citing 75 incidences of liver damage in alcohol abusers who consumed acetaminophen for therapeutic reasons (Refs. 1 through 27), the comment asserted that the reports strongly suggest that alcohol abuse potentiates acetaminophen's liver toxicity.

The comment stated that the clinical observation of increased liver toxicity of acetaminophen in alcohol abusers has been confirmed by experimental data in animals and humans (Refs. 22 and 28 through 46). In the comment's view, these experimental data demonstrate that: (1) Alcohol has a significant effect on acetaminophen metabolism; (2) chronic alcohol ingestion has been shown to induce microsomal enzymes, thereby increasing the formation of the toxic intermediate metabolite of acetaminophen, known as *N*-acetyl-*p*-benzoquinoneimine (NAPQI); and (3) chronic alcohol ingestion interferes with the detoxification of NAPQI by depleting hepatic glutathione (GSH).

Citing information indicating that alcohol is consumed by two-thirds of the American population (12 percent of this population considered to be heavy drinkers (Ref. 47) and that acetaminophen is widely available (present in over 200 OTC drug products), the comment asserted that the concurrent use of alcohol and acetaminophen can be predicted to be extraordinarily common. The comment suggested that the use of acetaminophen with alcohol may be even greater because heavy promotion stating that acetaminophen causes less stomach irritation than aspirin has made it the preferred OTC internal analgesic/antipyretic used in the presence of alcohol-related gastric upset. The comment asserted that these new data suggest that alcohol abusers appear to be at greater risk of hepatotoxicity from the therapeutic use of acetaminophen. Accordingly, the comment recommended that the labeling of these OTC drug products be strengthened to

ensure that consumers who abuse alcohol are not exposed to unnecessary daily use of acetaminophen. The comment added that warnings concerning the use of acetaminophen by alcohol abusers are included in the United States Pharmacopeial Dispensing Information (Refs. 48 and 49).

In addition to its proposed warning, the comment suggested that the maximum daily dose of acetaminophen be reduced from 4 to 2 grams (g) per day for this segment of the population. However, the comment did not provide data to support the reduced maximum daily dose. The comment recommended the following revision to the dosing directions proposed for acetaminophen in § 343.50(d)(2) (21 CFR 343.50(d)(2)) of the tentative final monograph: "If you drink large amounts of alcoholic beverages regularly, do not exceed 2 grams of acetaminophen (4 to 6 tablets) a day."

The comment subsequently submitted additional data to support its recommendations that included the following: (1) Reports of acetaminophen hepatotoxicity in alcohol abusers or associated with Psittacosis (Refs. 50 through 53), (2) a retrospective study of the effects of chronic alcohol intake on the prognosis and outcome of acetaminophen overdose (Ref. 54), and (3) a study of acetaminophen metabolism in alcohol abusers (Ref. 55).

Two comments disagreed with the need for the proposed warning, arguing that the existing data provide no rational basis for a warning. Citing its review of the scientific literature (Ref. 56), one comment questioned the number of cases of acetaminophen-induced liver toxicity due to the ingredient's therapeutic use by alcohol abusers. The comment stated that the majority of the reports involved subjects with a history of alcohol abuse and use of amounts of acetaminophen far in excess of the maximum daily therapeutic dose. The comment contended that the reliability of the history of acetaminophen use and the regularity of dosing included in these reports was questionable. The comment cited six additional published articles (Refs. 57 through 62) containing reports of acetaminophen-induced liver toxicity in alcohol abusers and contended that none of these reports supports an alcohol warning.

One of the comments disagreed with the assertion that experimental data in animals and humans have demonstrated chronic microsomal induction or increased NAPQI production in association with acetaminophen-alcohol use. The comment cited studies by Critchley et al. (Refs. 63 and 64) and Lauterberg and Velez (Ref. 65) in which no evidence of microsomal induction was found in heavy drinkers. Moreover, the comment cited additional studies (Refs. 66, 67, and 68) that it asserted demonstrated a reduction of microsomal enzyme activity in subjects with liver disease (including alcoholic hepatitis). The comment noted the results of a study in mice by Mitchell et al. (Ref. 35) that demonstrated for covalent binding or hepatic necrosis to occur GSH levels need to be reduced to approximately 20 to 30 percent of normal. The comment asserted that a reduction of such magnitude is unlikely except in severe malnutrition. Concerning the cited animal data, the comment noted that in the vast majority of studies the amounts of acetaminophen ingested would correspond to overdose amounts in humans.

The comment concluded by stating that the safety profile of acetaminophen in alcohol abusers should be evaluated in the context of their inclination to develop gastritis, gastroduodenal ulceration, hepatic cirrhosis, impairment of coagulation mechanisms, portal hypertension, and GI hemorrhage. Citing the fact that doctors frequently recommend acetaminophen to their alcohol abusing patients because it does not cause GI irritation or have platelet inhibiting effects, the comment asserted that an alcohol warning for OTC drug products containing acetaminophen would be contrary to the public interest. The comment suggested that such a warning might encourage individuals who abuse alcohol to use other OTC internal analgesic/antipyretic drug products containing ingredients that carry a greater risk of injury.

III. The Advisory Committees Meetings

The agency subsequently asked NDAC for advice on the need for an alcohol warning for OTC drug products containing acetaminophen. On June 29, 1993, NDAC met to consider the issue. The agency provided NDAC the following data and information: (1) The history of the agency's evaluation of the issue, (2) a summary of issues raised by comments in response to the tentative final monograph, (3) published reports of acetaminophen-induced liver toxicity in alcohol users at various acetaminophen doses, (4) data on the pharmacokinetics of acetaminophen metabolism in alcohol abusers, (5) data on microsomal enzyme induction in subjects with liver disease, (6) epidemiological data on the effect of alcohol abuse on acetaminophen overdose, (7) animal data on the effects of ethanol on acetaminophen metabolism, and (8) animal studies of the effect of diet on glutathione levels. A copy of this information is on file in the Dockets Management Branch (Ref. 69). Interested parties were also given the opportunity to present their positions.

The agency asked NDAC to consider: (1) Whether the data supported the need for an alcohol warning for OTC drug products containing acetaminophen; (2) the population at risk in terms of alcohol consumption, e.g., people who rarely drink, social drinkers, or alcohol abusers, and the acetaminophen dose ingested; (3) any special benefit/risk considerations concerning the use of an alcohol warning in the population at risk, e.g., will alcohol abusers switch to other OTC internal analgesic/antipyretic ingredients that have equivalent or greater risks; (4) the type of information that should be included in an alcohol warning, e.g., organ-specific information, description of alcohol amount, or other information; (5) whether the data are sufficient to support a reduced maximum daily acetaminophen dose for alcohol abusers; and (6) if so, what the reduced maximum daily dose should be.

NDAC concluded that alcohol abusers or heavy drinkers are at increased risk for developing liver toxicity when using acetaminophen. Based on this conclusion, NDAC recommended that an alcohol warning informing heavy alcohol users or abusers of their increased risk from the use of acetaminophen be included in the labeling of such products. Recommending that the exact wording of such a warning be developed by the agency, NDAC advised that the warning should specifically refer to possible liver damage. However, NDAC did not recommend a reduced maximum daily dose of acetaminophen for alcohol abusers. NDAC was concerned that an alcohol warning on OTC drug products containing acetaminophen in the absence of a similar warning on products containing other internal analgesic/antipyretic ingredients would cause alcohol abusers to switch to products containing those other ingredients, which may have equivalent or greater risks. Therefore, NDAC recommended that the agency not implement an alcohol warning for OTC drug products containing acetaminophen until NDAC had a chance to consider data on the risk of alcohol use with other internal analgesic/antipyretic ingredients (Ref. 70).

On September 8, 1993, NDAC and ADAC (the Committees) met jointly to consider data on the risk of the use of aspirin and other OTC analgesics by

heavy alcohol users or abusers. The agency provided the Committees the following data and information: (1) Published and unpublished epidemiological data on the risk of upper GI bleeding associated with the use of alcohol and aspirin, ibuprofen, and naproxen sodium; (2) data on the additive effects of these ingredients and alcohol on the GI tract; (3) data on the ability of alcohol to potentiate aspirin-prolonged bleeding times; (4) data on the effect of aspirin on ethanol pharmacokinetics; and (5) the Panel's conclusions on the safety of the OTC use of acetaminophen, aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. A copy of this information is on file in the Dockets Management Branch (Ref. 71). Interested parties were also given the opportunity to present their positions.

The agency asked the Committees to consider the following in evaluating the data: (1) Whether the data are sufficient to support an alcohol warning for OTC drug products containing aspirin, ibuprofen, and naproxen sodium; (2) whether the data are sufficient to support an alcohol warning for other salicylates (carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate); (3) the type of information an alcohol warning should include, i.e., organ specific information or statement of risk; and (4) the type of information that should appear in the labeling of combination drug products containing aspirin and acetaminophen.

The Committees concluded that the use of aspirin, ibuprofen, and naproxen sodium increases the risk of upper GI bleeding in heavy alcohol users or abusers. Concerning whether the data support an alcohol warning for OTC drug products containing these ingredients, the Committees voted 12 yes, 2 no for aspirin; 12 yes, 2 no for ibuprofen, and 12 yes, 1 no, and 1 abstention for naproxen sodium. The Committees further concluded that there are no data to support a warning for nonaspirin salicylates and, therefore, a recommendation on the need for an alcohol warning for these OTC drug products was outside their advisory scope. Regarding the type of information that should be included in an alcohol warning, the Committees recommended that the warning not mention a specified level of alcohol consumption, but were unable to reach a consensus whether the warning should be general or organ-specific (Ref. 72).

IV. Summary of Comments on the Committees' Recommendations

In response to the Committees' recommendations, the agency received 11 comments. Several comments from a manufacturers' association urged the agency to reject the Committees' recommendation for an alcohol warning for OTC aspirin drug products. One comment suggested that such a warning may jeopardize the compliance of individuals on low-dose aspirin regimens for cardiovascular indications. Other comments contended that the recommendation was not supported by reliable scientific data, but reflected concerns about unsubstantiated risks from the use of aspirin by individuals with a history of alcohol use. These concerns, the comments asserted, were based on submissions that included inaccurate summaries of studies without raw data and erroneous projections of morbidity and mortality based on incorrect assumptions. The comment suggested that these distortions had a significant impact on the Committees' recommendations.

In support of its contentions, the comment noted: (1) Criticisms of the available published data made by some Committee members during deliberations, and (2) specific comments made by an agency reviewer concerning unpublished epidemiological data presented to the Committees (Ref. 73). The comment pointed out that most of the studies were uniformly rejected by the Committees' members or the agency's reviewer, and thus the meeting produced no reliable evidence on which to justify a label warning regulation.

The comments also included critical assessments of the unpublished epidemiological data presented to the Committees: (1) A prospective observational study (Ref. 74), (2) a retrospective study of adverse drug reaction reports (Ref. 75), (3) a study conducted at the SUNY-Health Science Center (Ref. 76), (4) a study conducted at the Sloane Epidemiology Unit (Ref. 77), (5) a study conducted by Strom (Ref. 78), and (6) a study conducted at the University of Newcastle (Ref. 79). The comments contended that, based on these criticisms, the data from these studies could not be relied upon to support the need for an alcohol warning for OTC aspirin drug products. The comments asserted that an independent analysis of the data from two of the epidemiological studies (Refs. 77 and 79) is necessary to verify the studies' conclusions and requested that the agency obtain the raw data from the studies.

The comments asserted that the Committees misunderstood the agency's proposed warning in § 343.50(c)(1)(v)(B) that advises against the use of aspirin by persons that have stomach problems that persist or recur, or have ulcers, or bleeding problems, without consulting a doctor. The comments noted that most of the data submitted related to upper GI bleeding by persons with existing GI disease. The comments advised FDA to base its decision on the available scientific data and concluded that those data do not demonstrate that heavy alcohol users or abusers, with no preexisting ulcers or recurrent stomach or bleeding problems, are at an increased risk of upper GI bleeding from the use of OTC aspirin drug products.

In response to the comments' assertions, the agency received reply comments from members of the Committees (Ref. 80). One member stated that the Committees' final decision was based on the information available and was justified. Another member contended that if acetaminophen is to have a warning, then all OTC internal analgesic/antipyretic drug products should have a warning, preferably the same for all products. A third member expressed disagreement with the Committees' recommendation, explaining that a test of enhanced risk should be an odds ratio substantially greater than one. The member further recommended that an odds ratio of two or greater should be required, and the difference from one should be statistically significant.

A number of comments from the investigators for three of the unpublished epidemiological studies presented to the Committees addressed point by point the criticisms raised about the studies. These comments concluded that the data from these studies support the need for an alcohol warning. Another comment concluded that the data from these studies show that: (1) There is an increased risk of major upper GI bleeding in aspirin users that is independent of alcohol use, (2) there is an increased risk of major upper GI bleeding in alcohol users that is independent of aspirin use, and 3) aspirin further increases this risk in alcohol users.

V. The Agency's Tentative Conclusions on the Committees' Recommendations

A. Acetaminophen

After considering NDAC's recommendations and all available data and information, the agency has determined that the data are sufficient to warrant an alcohol warning for OTC drug products containing

acetaminophen. Based on an evaluation of the scientific literature, the agency has determined that individuals with a history of heavy alcohol use or abuse have an increased risk from the hepatotoxic effects of acetaminophen. In order to advise consumers with such a history to consult a physician for advice on the use of OTC acetaminophen drug products, the agency is proposing that OTC analgesic/antipyretic drug products containing acetaminophen bear an alcohol warning.

Acetaminophen is considered a dose dependent hepatotoxin (Ref. 81). Acute doses of acetaminophen of 15 g or more in adults have been associated with hepatotoxicity (Refs. 81 and 82). However, the scientific literature from 1966 to the present contains at least 97 reports of hepatotoxicity attributed to the ingestion of less than 15 g of acetaminophen (Refs. 1 through 27, 51, 52, 53, 57 through 62, and 83 through 93). With few exceptions, these case reports describe a clinical and laboratory picture consistent with acetaminophen overdose: Nausea, vomiting, hematemesis (bloody vomitus), jaundice, markedly elevated liver enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), elevated bilirubin, prolonged prothrombin time, and liver biopsy results (when obtained) demonstrating centrilobular necrosis.

Seventy-one of the 97 cases (73 percent) involve a history of heavy alcohol use or abuse (Refs. 1, 2, 3, 5 through 20, 22 through 26, 52, 53, 57 through 62, 86, 87, and 93). While a number of these reports lack sufficient information to permit a detailed assessment, the long history of the reports, their diverse countries of origin, consistent presentation and pattern of usage suggest that individuals with a history of heavy alcohol use or abuse are more susceptible to acetaminophen's hepatotoxic effects. Further, a majority of the 71 cases (41 cases or 58 percent) are associated with acetaminophen doses at or below the currently proposed maximum daily OTC dose (4 g per day) or moderate overdoses of approximately 6 g (Refs. 7, 12 through 18, 20, 22, 23, 24, 26, 52, 53, 57, 58, 60, 61, 62, 86, 87, and 93).

A number of these cases provide sufficient detail to suggest acetaminophen induced hepatotoxicity in heavy alcohol users or abusers at acetaminophen doses of 6 g or below. Bell, Schonsby, and Raknerud (Ref. 57) reported a 32-year-old male "periodic alcoholic" (patient 3) who began drinking after a period of abstinence, used acetaminophen to treat withdrawal symptoms, and took 3.4 g acetaminophen per day for 5 days prior to hospital admission. On the day of admission, the patient developed nausea and hematemesis. Jaundice and bruising were also observed.

Laboratory tests revealed elevated liver enzymes (AST 13,420 International Units/Liter (IU/L) and ALT 7,510 IU/L (reference AST and ALT 10 to 40 IU/L)) and hyperbilirubinemia (297 micromole/liter (μmole/L) or 17.4 milligrams (mg)/deciliter (dL) (reference bilirubin 3 to 25 μmole/L or 0.2 to 1.5 mg/dL)). Tests for hepatitis C surface antigen, hepatitis A and cytomegalovirus antibody, and Monospot were negative. The serum acetaminophen level 2 days after the last dose was 2.5 micrograms/milliliter (μg/mL). No liver biopsy was done. N-acetylcysteine (NAC) was not administered. The patient improved with supportive treatment and was discharged. At outpatient followup, 5 weeks after admission, all laboratory tests were normal.

Bell, Schonsby, and Raknerud (Ref. 57) also reported a 57-year-old woman (patient 4) with a history of gout who ingested 40 to 50 g of alcohol a day. For several years, she had taken 400 mg acetaminophen and 5 mg prednisone per day. In response to an increase in leg pain, she increased her intake to 2.4 to 3.2 g acetaminophen per day for several days. On the day of hospital admission, she vomited blood and developed symptoms compatible with hepatic encephalopathy (jaundice, somnolence, and bruising).

Laboratory tests revealed elevated aminotransferases (AST 16,180 IU/L and ALT 8,950 IU/L). Bilirubin was 123 μmole/L or 7.2 mg/dL. NAC was not administered. The patient died the day following admission with massive hematemesis and hypotension. Autopsy revealed abundant blood in the stomach and intestines but no sign of an ulcer. Microscopically, a marked centrilobular liver cell necrosis was seen.

Floren, Thesleff, and Nilsson (Ref. 7) described hepatotoxicity in a 58-year-old woman (patient 1) who regularly consumed a bottle of red wine a day. The patient was hospitalized due to a slight intoxication. Before admission, she admitted to ingesting 1 to 1.5 g acetaminophen, sedatives (oxazepam), and antidepressants (lorazepam) for an unspecified period of time. The patient was transferred from the psychiatric ward to the medical clinic due to elevated liver enzymes (AST 14.3 microkatal/L (μkat/L) and ALT 14.0 μkat/L). Reference levels for AST and ALT were less than 0.7 μkat/L.

At the time of transfer, the concentration of acetaminophen in serum was not measurable and NAC was not administered. Tests for hepatitis B surface antigen and hepatitis A were negative. A liver biopsy demonstrated centrilobular necrosis with normal portal zones. The biopsy revealed no evidence of steatosis, fibrosis, or cirrhosis. The patient recovered uneventfully.

Licht, Seeff, and Zimmerman (Ref. 20) reported a 53-year-old man who ingested 2.6 to 3.9 g acetaminophen daily for an undisclosed period of time. He admitted to a 15-year history of excessive alcohol intake with a recent intake of 2 quarts of whiskey daily. He entered the hospital after 3 days of weakness, abdominal discomfort, and jaundice.

Laboratory values at the time of admission indicated markedly elevated liver enzymes (AST 19,710 milliunits (mU)/mL) and ALT 4,560 mU/mL), a bilirubin of 13 mg/dL, and a prolonged prothrombin time of 22 seconds (control 10 seconds). A serum acetaminophen level obtained 12 hours after ingestion was in the nontoxic range (2 μg/mL). A test for hepatitis B surface antigen was negative. No liver biopsy was obtained. NAC was not administered. The patient recovered.

Luquel et al. (Ref. 60) described a 49-year-old man who was admitted to the hospital with confusion, hematemesis, and decreased urine output. In addition to increasing his beer intake, he also took 1.2 g acetaminophen and 25 mg ethyl loflazepate for 2 days prior to hospitalization. Laboratory values were AST 1,870 IU/L, ALT 640 IU/L, total bilirubin 39 μmole/L or 2.3 mg/dL, and a prothrombin rate of 75 percent. No serum acetaminophen was detected, and NAC was not administered. The results of a liver biopsy performed on the third day of hospitalization revealed centrilobular necrosis. The patient recovered uneventfully.

Seeff et al. (Ref. 26) reported six cases of acetaminophen hepatotoxicity in alcohol abusers. Three cases (patients 2, 3, and 6) involved doses of approximately 4 g acetaminophen. Patient 2 was a 30-year-old male chronic alcohol abuser who ingested 12.5 g acetaminophen over a 3-day period for pain related to a dental abscess. (Assuming that the doses were evenly distributed over the 3 days, he ingested approximately 4.2 g acetaminophen per day.) His laboratory values showed elevated liver enzyme[illegible] greater than 10,000 IU/L and ALT 7,610 IU/L), a bilirubin of 2.4 mg/dL, and a prothrombin time 9.3 seconds longer than control. A test for hepatitis B surface antigen was negative. Serum acetaminophen level and liver biopsy

were not done. The patient was treated with NAC, improved, and was released from the hospital.

Patient 3 was a 39-year-old man who was hospitalized for a submandibular infection following a fracture. Over a 1-week period, he had taken approximately 3.8 g acetaminophen per day. On admission, his laboratory values revealed elevated liver enzymes (AST 5,640 IU/L and ALT 354 IU/L), bilirubin 16.5 mg/dL, and a prothrombin time twice the control. Serum acetaminophen levels were not determined, nor was a liver biopsy performed. NAC was not administered. The patient improved over the next few weeks and was discharged.

Patient 6 was admitted to the hospital for acute alcohol withdrawal syndrome. During the 3 days prior to admission, she took approximately 3.7 g acetaminophen a day for headache. Laboratory values included AST 6,888 IU/L, ALT 2,480 IU/L, total bilirubin 6.6 mg/dL, and a prothrombin time 10 seconds longer than control. Serum acetaminophen level, liver biopsy, and viral screening were not performed. NAC was not administered and with supportive treatment, the patient recovered.

Edwards and Oliphant (Ref. 86) described a 46-year-old man who presented to the hospital with a 2-hour history of epigastric pain with hematemesis. The patient gave a history of regular alcohol consumption. In the week prior to admission, he had consumed two 1,250 mL spirits over the week and 12 cans of beer daily and concurrently taken not more than 3 g of acetaminophen daily for hangover, up to a total dosage of 18 g. He took an additional 3 g of acetaminophen 6 hours prior to his admission to the hospital.

Liver function tests conducted on day 2 of hospitalization showed markedly abnormal aminotransferases (AST 30,000 IU/L and ALT 9,750 IU/L) and a bilirubin of 86 µmole/L or 5 mg/dL. At 6 hours post ingestion, the serum acetaminophen level was 0.04 µg/mL. On day 2 the level was 0.005 µg/mL. Hepatitis serology was negative for hepatitis A, B, and C. No liver biopsy was performed. NAC was not administered. The patient's convalescence was slow but uneventful.

Johnson, Friedman, and Mitch (Ref. 12) described a 23-year-old female alcohol abuser who developed acute hepatitis and renal failure 3 days after ingesting a bottle of cold medication containing 6 g acetaminophen in 25 percent alcohol. The patient's medical history included a previous hepatitis infection. Laboratory values at admission were AST 4,320 IU/L, ALT 1,130 IU/L, total serum bilirubin 10 mg/dL, and a prothrombin time of 13.1 seconds (control 12 seconds). Serum acetaminophen was undetectable 6 days after acetaminophen ingestion. A test for hepatitis B surface antigen was negative. Antibodies to hepatitis B surface antigen were detected. No liver biopsy was conducted. NAC was not administered. Hepatic function gradually improved and the patient was discharged.

Kartsonis, Reddy, and Schiff (Ref. 13) reported a 39-year-old male alcohol abuser who developed vague inguinal discomfort and began self-medicating with 5 g acetaminophen per day over a 6-day period. He presented to the hospital with nausea, vomiting, and abdominal pain. Laboratory tests revealed elevated aminotransferases (AST more than 8,270 IU/L and ALT 6,494 IU/L), total bilirubin 4.2 mg/dL, and an extended prothrombin time of 21 seconds (control 12 seconds). Acetaminophen was not detectable in the blood. Neither a liver biopsy nor viral screening were done. NAC was not administered. The man had an uneventful recovery with supportive care and was discharged from the hospital after 7 days.

O'Dell, Zetterman, and Burnett (Ref. 24) reported a 38-year-old woman who took 6 g acetaminophen for 5 days for stomach pain. She had a history of chronic pancreatitis and chronic alcoholism (approximately 200 g ethanol a day for 10 years). She presented to the hospital with nausea, vomiting, and abdominal pain. Liver enzymes on admission were AST 1,512 IU/L and ALT 554 IU/L. Bilirubin levels and prothrombin times were normal. Acetaminophen blood levels were not determined. A liver biopsy revealed centrilobular necrosis without signs of alcoholic hepatitis or centrilobular fibrosis.

Acetaminophen administration was discontinued and liver enzymes returned to normal. The patient was counseled about acetaminophen and alcohol toxicity, and discharged. Subsequently, she was readmitted to the hospital with abdominal pain of 2 weeks duration for which she had taken 6 g acetaminophen a day.

On admission, her liver enzymes were AST 5,210 IU/L and ALT 1,580 IU/L, and total bilirubin was 1.1 mg/dL. A serum acetaminophen level was not determined. A second biopsy showed extensive centrilobular fibrosis. Alcoholic hyalin and polymorphonuclear leukocyte inflammation were not observed. The periportal regions were normal and there was no portal fibrosis. The patient recovered and was discharged from the hospital.

Seeff et al. (Ref. 26) reported a 58-year-old male chronic alcohol abuser hospitalized for alcoholic hepatitis and cervical neck pain. The patient's history included a recent increase in alcohol consumption and chronic ingestion of 4 to 6 g acetaminophen daily for an unspecified period of time. On admission, AST was 2,870 IU/L, bilirubin was 3.6 mg/dL, and prothrombin time was 14 seconds (control 11.3 seconds). ALT was not reported, and serum acetaminophen levels were not determined. NAC was not administered. Laboratory values on the next day included an AST level of 790 IU/L and an ALT level of 2,300 IU/L. Serologic tests for hepatitis B were negative. No liver biopsy was done. Serum aminotransferases and prothrombin time returned to normal, and the patient was discharged 12 days after admission.

Kumar and Rex (Ref. 52) reported six cases of hepatotoxicity, four of which involved acetaminophen doses of 5 to 6 g. Case 2 was a 65-year-old female alcohol abuser admitted to the hospital after 1 day of vomiting. Her admitting AST and ALT levels were 3,199 IU/L and 1,270 IU/L, respectively. Her total bilirubin level peaked at 41 µmole/L or 2.4 mg/dL. After 2 days of observation and improvement, it was discovered that she had been taking about 6 g/day acetaminophen for back pain. Serum acetaminophen level, liver biopsy, and viral screening were not done. She was discharged in stable condition with near normal liver test results.

Case 3 was a 43-year-old woman admitted to the hospital with a 6-day history of fatigue, malaise, nausea, and vomiting. Peak laboratory values included elevated liver enzymes (AST 14,920 IU/L and ALT 3,304 IU/L), total bilirubin 126 µmole/L or 7.4 mg/dL, and a prothrombin time of 46 seconds (no control reported). No serum acetaminophen levels, liver biopsy, or viral screening was performed. Initially, the woman denied alcohol or acetaminophen use. However, a friend subsequently reported that she was a heavy drinker and had been taking 5 g acetaminophen daily for an unspecified period of time. NAC was not administered, and she was discharged in stable condition.

Kumar and Rex (Ref. 52) also described a 55-year-old man (case 4) with a history of heavy alcohol use who was hospitalized after 3 to 4 weeks of nausea and vomiting. On admission, laboratory values included elevated liver enzymes (AST 1,240 IU/L and ALT 252 IU/L), total bilirubin 35 µmoles/L,

and a prothrombin time of 15 seconds (no control reported). His liver enzyme levels peaked on day 2 (AST 7,225 IU/L and ALT 1,280 IU/L). It was later determined that he had ingested 6 g acetaminophen daily for an unspecified period of time for headaches and arthritic pain. Serum acetaminophen level, viral screening, and liver biopsy were not done. The patient was discharged after 20 days with normal liver function tests.

Another case reported by Kumar and Rex (Ref. 52) was a 59-year-old male alcohol abuser (case 5) who was admitted to the hospital with dizziness and orthostatic hypotension. He reported ingesting 5 g acetaminophen daily for 1 month for hip pain. Peak liver test abnormalities were present on the day of admission (AST 3,000 IU/L, ALT 290 IU/L, total bilirubin 133 μmole/L, and prothrombin time 19 seconds, no control reported). Serum acetaminophen levels, liver biopsy, and viral screening were not done. NAC was not administered. The patient subsequently developed sepsis and GI bleeding and died 2 weeks after hospitalization.

The agency subsequently received an additional 19 reports of acetaminophen liver toxicity (Ref. 94). Fifteen of these reports involved acetaminophen doses of less than 6 g daily in individuals with a history of moderate to heavy alcohol use. Five of the reports (case numbers 9, 11, 12, 13, and 19) provided sufficient detail to suggest acetaminophen-induced hepatotoxicity.

Case number 9 was a 45-year-old woman with a history of alcohol abuse who, at the time of admission, had a history of ingesting one to two glasses of wine daily (only at night). The patient had a history of acetaminophen use along with alcohol. For approximately 5 days prior to admission, the patient reportedly took acetaminophen at the recommended dose (4 g per day) for flu-like symptoms. The patient vomited (some "coffee ground" emesis) for 5 days prior to admission, and for 2 days had a progressive deterioration of mental status. On the night prior to admission, she became delirious and was brought to the emergency room.

Laboratory values showed grossly elevated liver enzymes (AST 15,205 IU/L and ALT 4,051 IU/L), a prothrombin time of 63.7 seconds (no control reported), and a total bilirubin of 3.8 mg/dL. The serum acetaminophen level was 12 μg/mL (time after last dose unknown). No record of hepatitis screening was provided. During the hospital stay, an upper endoscopy showed bleeding secondary to diffuse gastritis and portal gastropathy. The patient continued to deteriorate and died 1 month after hospital admission. Autopsy findings included diffuse hepatic necrosis with micro vesicular fat and bile stasis.

Case number 11 was a 43-year-old man with a long-standing history of alcohol abuse (at least 12 cans of beer daily for 16 years). He developed lower abdominal pain and fever, followed 2 days later by nausea and vomiting, for which he took two medications containing acetaminophen (estimated dose less than 4 g per day) for at least 1 day. He was admitted to the hospital 2 days later with hypotension and abnormal liver and renal function.

Laboratory values showed elevated liver enzymes (AST 5,450 IU/L and ALT 2,251 IU/L) a prothrombin time of 55.9 seconds (no control reported), and a total bilirubin of 89 μmole/L. The serum acetaminophen level was 5 μg/mL (time after last dose unknown). The patient died 10 days after admission to the hospital. No record of hepatitis screening was provided. Post-mortem findings included centrilobular necrosis and widespread mucosal hemorrhages consistent with coagulopathy. The autopsy report noted that while there was no evidence of cirrhosis, the presence of ascites, muscle wasting, and testicular wasting was consistent with the effect of chronic liver disease.

Case number 12 was a 41-year-old man who had taken acetaminophen-containing drugs for 2 days (4 to 5 g/day) to alleviate the pain of fractured ribs. He had a history of alcohol abuse and had recently been drinking 12 beers a day. He was admitted to the hospital with complaints of shortness of breath and left-side chest pain. On examination, he was found to have greater than an 80-percent pneumothorax of the left lung and was also deeply jaundiced. A blood alcohol level done at time of admission was reported as "0."

Laboratory findings included AST 21,900 IU/L, ALT 11,200 IU/L, total bilirubin 17.8 mg/dL, and a prothrombin time of 40 seconds (no control reported). The serum acetaminophen level was 2.1 μg/mL 4 days after the last acetaminophen ingestion. The results of screening for hepatitis A antibody, hepatitis B surface antigen and antibody, and hepatitis B core antibody were negative. Screening for Epstein-Barr surface antigen was also negative. A liver biopsy showed fulminant hepatic necrosis with mild to moderate evidence of alcohol-related liver disease. A diagnosis of acute toxic liver failure was made, and the patient was transferred to a second hospital for a liver transplant, which was done within 72 hours of transfer. Following the transplant, the patient was discharged in stable condition. Sections of the removed liver showed extensive centrilobular necrosis, with up to 50 or 60 percent necrosis in some areas.

Case number 13 was a 62-year-old man with a history of heavy alcohol use and severe steroid-dependent chronic obstructive pulmonary disease. He subsequently reduced his alcohol intake to two to four beers a day for several years. A few days prior to admission, he developed flu-like symptoms (sore throat, myalgia, and sleeping difficulty) for which he took an estimated 4 to 5 g acetaminophen over an 8-hour period. He became progressively weaker and fell on the day prior to admission.

On admission, he was found to have hypotension, weakness, grossly elevated liver function tests (AST 16,279 IU/L, ALT 10,942 IU/L, a total bilirubin of 7.8 mg/dL, and a prothrombin time of 55.7 seconds, no control reported). Serum acetaminophen levels were not determined. The patient was diagnosed with acute hepatic failure and died within 24 hours of admission. A post-mortem liver biopsy revealed massive hepatocellular necrosis.

Case number 19 was a 30-year-old man with a history of occasional alcohol use. Four days prior to admission, he developed malaise and a sore throat and drank six glasses of wine prior to retiring for the evening. His symptoms became progressively worse, and he took acetaminophen (4 g per day) for 3 to 4 days. On the morning of admission, he became disoriented, unable to speak, and agitated.

Admission laboratory data revealed markedly elevated liver enzymes (AST 13,580 and ALT 11,250 IU/L), a prothrombin time of 32.4 seconds (no control reported), and a bilirubin of 7.0 mg/dL. No blood alcohol was detected. A serum acetaminophen level of 7 μg/mL was obtained approximately 48 hours after the last acetaminophen dose. Screening for hepatitis B surface antigen and core antibody was negative. Tests for herpes simplex virus were initially negative but were positive after transfusions. The patient deteriorated rapidly and lapsed into a coma. A liver transplant was done, after which the patient was initially stable, but subsequently developed deteriorating kidney function. The liver pathology report described extensive centrilobular hemorrhagic necrosis.

Zimmerman and Maddrey (Ref. 95) reported 67 additional cases of hepatic injury in regular alcohol users associated with the use of acetaminophen for therapeutic purposes. The majority of cases

involved subjects considered to be alcohol abusers or who reported alcohol intakes of at least 60 g/day. In 27 of the cases (40 percent), hepatic injury was attributed to acetaminophen doses under 4 g/day. In another 13 cases (19.4 percent), hepatic injury was associated with acetaminophen doses of 4.1 to 6 g/day. Unfortunately, specific details of the individual cases were not provided. Thus, a definitive assessment of the role of acetaminophen in the reported liver injuries is difficult.

Acetaminophen is metabolized principally by glucuronide and sulphate conjugation in the liver. When acetaminophen is taken at therapeutic doses, glucuronide and sulphate metabolites account for 80 to 90 percent of the acetaminophen metabolites in urine (Ref. 80). Ordinarily, a small fraction of acetaminophen is metabolized by microsomal enzyme cytochrome P450 2E1 to NAPQI (Ref. 96), but if the capacity of the glucuronidation and sulfation metabolic pathways is exceeded, as in overdose, or if the synthesis of P450 2E1 is induced, increased amounts of NAPQI are produced.

NAPQI is avidly electrophilic and can bind to liver cell macromolecules, disrupt cell function, and ultimately cause liver cell death. The binding of NAPQI to liver cell components is prevented if the compound is detoxified by conjugation with GSH or other sulfhydryl compound. The detoxification of NAPQI generates, through a series of reactions, mercapturic acid and cysteine metabolites. GSH is depleted in the detoxification process and must be replenished by sulfhydryl compounds from the diet or by drugs given as therapy, e.g., the cysteine containing compound NAC. NAC has well-documented effectiveness as an antidote for acetaminophen overdose. More recently, it has been recommended for the treatment of acetaminophen liver toxicity after ingestion of therapeutic doses of acetaminophen by individuals with a history of heavy alcohol use or abuse (Ref. 95).

Pharmacokinetic studies in humans suggest an increased sensitivity of heavy alcohol users or abusers to the hepatotoxic effects of acetaminophen. The data suggest that the ingestion of even relatively small doses of acetaminophen (1 g) by heavy alcohol users or abusers results in a higher than normal percentage of acetaminophen metabolized by the microsomal enzyme pathway that yields NAPQI. The available pharmacokinetic data suggest that the rate of metabolism of acetaminophen is increased in alcohol abusers (as evidenced by an increase in the plasma clearance rate (CL) and a decrease in the plasma elimination half-life of acetaminophen ($t_{1/2}$)). This increased metabolism suggests increased activity of the microsomal pathway in this population.

Dietz et al. (Ref. 28) compared the metabolism of acetaminophen in six healthy alcohol abusers (240 to 480 mL alcohol daily for 2 to 40 years) to eight healthy nondrinking adults. The alcohol abusers had stopped drinking within the previous 48 hours. Baseline laboratory data were obtained from both groups. Following a 12-hour fast, a single 1 g dose of acetaminophen was administered. Blood samples were collected immediately before acetaminophen administration and at 30, 60, 90, 120, and 240 minutes thereafter. Acetaminophen plasma data were fit to a one-compartment open model for oral dosing using nonlinear regression analysis. The time to peak concentration (t_{max}), peak plasma concentration (C_{max}), the area under the concentration-time curve (AUC), and CL were determined. Laboratory screening data revealed significant differences between the controls and alcohol abusers only in gamma-glutamyl transpepsidase activity (12.6 units in controls and 204.7 units in alcohol abusers, $p = 0.01$). There was no significant difference in renal function between the two groups. The acetaminophen plasma AUC's for the groups were significantly different ($p < 0.01$). While both groups achieved C_{max} at approximately the same time, C_{max} for the nondrinkers was significantly higher than for the alcohol abusers (20.2 µg/mL versus 15.4 µg/mL). The CL was also significantly accelerated in the alcohol abusers (247.4 mL/minute (min) versus 154.4 mL/min, $p < 0.001$).

Girre et al. (Ref. 55) obtained similar results in a comparison of the pharmacokinetics of acetaminophen in 12 chronic alcohol abusers and 12 healthy controls. The mean daily alcohol consumption for the alcohol abusers was 210 ± 95 g of absolute alcohol for a mean duration of 14.5 ± 9.5 years. Control subjects drank only moderately (defined in the study as a weekly alcohol consumption < 80 g) and were asked to abstain from alcohol consumption for 36 hours before the trial. A single, 1-g acetaminophen dose was administered following a 12-hour fast. Blood samples were taken before acetaminophen intake and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours thereafter.

The following pharmacokinetic parameters were determined: C_{max}, t_{max}, AUC, CL, and $t_{1/2}$. A comparison of C_{max} and t_{max} showed no significant differences between the two groups. However, in the alcohol abusers, $t_{1/2}$ was significantly shorter than for the controls (1.71 versus 2.84 hours, $p < 0.05$). CL was increased in the alcohol abusers (30.34 versus 26.52 L/hour, $p < 0.05$).

Observed increases in the excretion of metabolites (mercapturate and cysteine) of the microsomal pathway also suggest increased activity of this pathway in this population. Villeneuve et al. (Ref. 27) observed an increased urinary excretion of cysteine and mercapturate metabolites of acetaminophen in alcohol abusers. The authors compared the pharmacokinetics of acetaminophen metabolism in nine alcohol abusers (457 ± 50 g ethanol per day for at least 3 months), eleven subjects with alcoholic cirrhosis, and six healthy normal subjects. Subjects in the control group consumed no alcohol or other medications.

Subjects with a history of alcohol abuse were selected based on the absence of alcoholic hepatitis or cirrhosis (determined by physical examination and standard biological tests for liver function) and the lack of drug use (other than alcohol). The diagnosis of cirrhosis was confirmed by liver biopsy. Cirrhotic subjects were hospitalized at the time of the study and did not consume alcohol for at least 30 days prior to the start of the study. Five of the cirrhotic subjects received spironolactone (100 mg/day) for treatment of their ascites.

After 12 hours of fasting, a liquid preparation of acetaminophen was administered orally at a dose of 12 mg/kilogram with 200 mL of water (mean dose: Controls 920 mg, alcohol abusers 805 mg, and cirrhotics 872 mg). Blood samples were taken at 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 420 minutes after ingesting acetaminophen. Urine was collected for 24 hours after ingestion. The apparent oral clearance (CL_o), AUC, and $t_{1/2}$ were determined.

The percentage of the acetaminophen dose eliminated in the urine of alcohol abusers was significantly decreased from the controls (88.6 to 63.4 percent). In the cirrhotics, clearance was decreased by 50 percent ($p < 0.05$), $t_{1/2}$ was extended ($p < 0.05$), and urinary elimination was not significantly decreased in relation to the controls. The level of glucuronide and sulfate conjugates in the alcohol abusers was not significantly different in comparison to the controls. The excretion of cysteine and mercapturate metabolites of acetaminophen was increased in a significant manner for the alcohol abusers ($p < 0.05$). When this increase

was expressed as a percent of the administered dose, the mean augmentation for the alcohol abusers was 92 percent. In cirrhotics, the profile of these metabolites was comparable to the controls.

An additional mechanism of the increased sensitivity of alcohol abusers to acetaminophen toxicity has been postulated to be a diminished capacity to detoxify NAPQI by conjugation with GSH. Lauterberg and Velez (Ref. 65) studied glutathione levels and the formation of the toxic metabolite of paracetamol (acetaminophen) in chronic alcohol abusers. Study subjects were recruited from an alcohol treatment program and had a history of heavy drinking (average consumption of 180 g ethanol per day) up to 2 days prior to study initiation. Some of these subjects received chlorodiazepoxide (last dose 10 mg more than 10 hours prior to the study) as part of their treatment. Control subjects denied consumption of alcohol in excess of 10 g/day and were not taking any medications.

The study determined the plasma GSH levels of alcohol abusers without clinical evidence of alcoholic liver disease and in controls following an overnight fast. The GSH plasma concentration was about 50 percent lower in alcohol abusers than in the controls (8.48 versus 4.35 micromoles (μmole), $p < 0.05$). In contrast, the plasma concentration of free cysteine was similar for alcohol abusers and for controls.

The study also examined the effect of acetaminophen administration on plasma GSH. Subjects were given a 2 g acetaminophen dose in lemonade after a 10-hour fast. Blood samples were taken hourly for 4 hours. Urine was collected for 6 hours. After the administration of acetaminophen, the plasma GSH concentration in controls was significantly decreased at 3 hours from a mean concentration of 8.37 to 6.26 μmole ($p < 0.02$ by paired t-test). The plasma GSH levels in alcohol abusers were significantly lower than baseline at 2 and 3 hours (3.10 and 2.40 μmole, respectively, baseline 4.66 μmole). All GSH levels in the alcohol abusers were significantly lower ($p < 0.05$) than the corresponding values in the control group. The decrease in plasma cysteine was not significantly different from control values. Urinary excretion of mercapturic acid and cysteine conjugates was slightly increased in alcohol abusers. However, the difference was not statistically significant. There was no significant difference in the relative amounts or proportions of glucuronide and sulfate metabolites between alcohol abusers and controls, suggesting no impact of alcohol abuse on these metabolic pathways.

To confirm that low plasma GSH levels reflect low intrahepatic GSH, the authors measured hepatic GSH in liver samples obtained from alcohol abusers in whom a percutaneous liver biopsy was indicated. The biopsied subjects all had histological evidence of alcoholic hepatitis with and without cirrhosis and had more severe liver disease than the alcohol abusers in whom plasma GSH was measured. The hepatic concentration of GSH in the biopsied subjects was about 50 percent lower than in subjects without liver disease and subjects with a mild inflammatory process or nonalcoholic cirrhosis.

Based on the data discussed above, the agency concludes that chronic heavy alcohol use or abuse has a significant effect on the metabolism of acetaminophen and the detoxification of acetaminophen's toxic metabolite, NAPQI. These changes put individuals with a history of heavy alcohol use or abuse at an increased risk from acetaminophen liver toxicity. Therefore, the agency believes that an alcohol warning for adult OTC internal analgesic/antipyretic drug products containing acetaminophen is warranted. However, the agency does not find the submitted data sufficient to demonstrate the safety of a lower maximum daily dose (2 g acetaminophen) in heavy alcohol users or abusers or to support a specific labeling recommendation to that effect. Therefore, the agency is not proposing a reduction in the recommended maximum OTC daily 4 g dose of acetaminophen at this time. Rather, the agency believes that OTC labeling should recommend contact with a physician to these individuals. A physician familiar with a consumer's history can advise them on whether a particular OTC analgesic/antipyretic drug product is appropriate for their use, suggest other appropriate therapies, and counsel them about their alcohol use.

B. Other Monograph Ingredients

The agency has carefully considered the Committees' recommendations, all comments received in response to those recommendations, and all available data and information and has determined that an alcohol warning for OTC internal analgesic/antipyretic drug products containing aspirin is warranted. The agency agrees with the comments that the unpublished epidemiological data presented to the Committees at the September 8, 1993, meeting alone were insufficient to document an increased risk of GI bleeding associated with aspirin use by individuals with a history of heavy alcohol use or abuse. At that meeting (Ref. 72), agency representatives stated that the unpublished studies had design problems and did not convince them that the use of alcohol with OTC internal analgesic/antipyretic ingredients (such as aspirin) can cause excess GI bleeding. Agency representatives also stated that, based on these studies, the magnitude of the risk and the confidence level of the estimated risk were uncertain.

However, the irritant effects of aspirin on the gastric mucosa are well documented. In discussing the effect of aspirin on the gastric mucosa (42 FR 35346 at 35386 to 35397), the Panel concluded that aspirin and salicylic acid have a direct local irritant effect on the surface of mucosal cells lining the GI tract. The Panel asserted that the acute use of aspirin may activate symptoms of both gastric and duodenal ulcer, such as epigastric pain and GI hemorrhage. The Panel stated that the initiation or exacerbation of stomach ulcers, stomach irritation, and intestinal inflammation occurs in a significant number of aspirin users. Individuals particularly at risk are those with a history of symptoms of GI problems.

Alcohol is also a gastric irritant. Tarnawski et al. (Ref. 97) studied the effect of the intragastric administration of 100 mL of 40 percent ethanol (the alcohol content of 80 proof whiskey) or saline in 15 healthy volunteers (ten test and five control subjects). Changes in the appearance of the gastric mucosa, mucosal histology, luminal pH, and gastric mucosal potential were evaluated. The authors found that a single dose of 40 percent alcohol produced rapid endoscopic changes (congestion and focal hemorrhages) and prominent histologic changes (exfoliation of the surface epithelium, edema of the lamina propria, and hemorrhagic lesions associated with mucosal microvascular damage). Histologic changes were seen as early as 5 minutes after alcohol administration.

Individuals with a history of heavy alcohol consumption commonly develop characteristic subepithelial hemorrhages with the endoscopic appearance of "blood under plastic wrap." Although termed "hemorrhagic gastritis," these lesions are composed of hemorrhage and edema in the interstitial space under the surface epithelium, without inflammation (Ref. 98). While there are no controlled studies demonstrating that ethanol in lower doses will precipitate relevant gastric hemorrhage, acute hemorrhagic gastritis accounts for 25 percent of the cases of major bleeding in alcohol

abusers compared to 5 percent in the population without a history of prior alcohol abuse (Ref. 99). As with gastritis from other causes, individuals with alcoholic gastritis may have no symptoms whatsoever (Ref. 100). Currently available data do not provide sufficient information to assess the magnitude of the risk of aspirin use by individuals with a history of heavy alcohol use or abuse.

Further, in the last 15 to 20 years, the use of aspirin for the prevention of recurrent myocardial infarction (MI), transient ischemic attacks (TIA), and stroke has become prevalent. The agency has evaluated the available literature on aspirin for cerebral vascular and cardiovascular indications and the incidence of GI bleeding and ulcers in these studies. Eighteen of the 19 studies that included aspirin and placebo groups and evaluated GI bleeding reported an increase in GI bleeds in the aspirin group when compared to the placebo group (Refs. 101 through 118). One study reported no GI bleeds in either group (Ref. 119). Aspirin dosages in the studies ranged from 75 to 1,500 mg daily. Increases in bleeding were reported at all aspirin dosage levels when compared to the control groups. The number of subjects in the studies ranged from 125 to 22,071. The overall results of these studies show that GI bleeding increases with long-term aspirin use, even at low aspirin doses.

The UK–TIA study (Ref. 106) suggested a risk of GI bleeding that increased in a dose-dependent manner. The odds ratio (95 percent confidence interval) was 3.3 (1.2 to 9.0) for 300 mg daily aspirin and 6.4 (2.5 to 16.5) for 1,200 mg daily aspirin (Ref. 120). Several studies reported the number of ulcers in the aspirin and placebo groups. The Aspirin Myocardial Infarction Study Research Group (Ref. 112) reported "symptoms suggestive of peptic ulcer, gastritis, or erosion of gastric mucosa" in 14.9 percent of the placebo group and in 23.7 percent of the aspirin group. The British Doctors' Study (Ref. 102) reported a significant increase in peptic ulcers in the aspirin group compared to the placebo group.

The Physicians' Health Study (a 325 mg aspirin dose on alternate days (Ref. 101) reported a nonsignificant increase in upper GI ulcers in the aspirin arm compared to placebo (169/11,037 versus 138/11,034, $p = 0.08$). However, a statistically significant increase in the number of duodenal ulcers was reported in the aspirin group (46/11,037 versus 27/11,034, $p = 0.03$), where most of the subjects reported some alcohol use (more than 70 percent of the subjects reporting daily or weekly use).

The agency is currently evaluating several new professional vascular uses of aspirin and is aware that more people are taking aspirin chronically for cardiovascular and/or cerebrovascular indications and thus may have an increased risk of GI bleeding or susceptibility to ulcers. Further, the magnitude of the risk of heavy alcohol use in this population is not clearly defined.

The agency is aware that numerous studies have examined the effects of alcohol consumption on the rate of cardiovascular disease. In a review of these studies, Marmot and Brunner (Ref. 121) concluded that the evidence suggests that two drinks a day do not cause cardiovascular harm and may be protective against coronary heart disease. Above two drinks per day, the authors found evidence of harmful effects. Heavier alcohol intakes have been associated with an increase in cardiovascular diseases, such as heart muscle disease, hypertension, disturbances in heart rhythm, and stroke (Ref. 122). Pohorecky (Ref. 123) found that the risk for hypertension among individuals drinking three to four drinks per day was 50 percent higher than among nondrinkers.

The American Heart Association (AHA) (Ref. 124) does not currently recommend the ingestion of moderate amounts of alcohol for its protective effect against cardiovascular disease. However, based on the adverse effects of alcohol on blood pressure, the AHA recommends that alcohol intake should not exceed two drinks per day (Ref. 124). The Dietary Guidelines of the U.S. Departments of Agriculture and Health and Human Services (Ref. 125) also recommend moderate alcohol consumption. These guidelines define moderate alcohol consumption as one drink (12 ounces (oz) of regular beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits) per day for women and two drinks per day for men. Based on these recommendations, the agency believes that the proposed warning provides appropriate advice to consumers on low-dose prophylactic aspirin regimens.

The agency acknowledges the Committees' conclusion that there are no clinical trial data supporting the need for an alcohol warning on OTC internal analgesic/antipyretic drug products containing carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. However, the agency is concerned that the absence of an alcohol warning on OTC drug products containing these ingredients may lead consumers to conclude that they are safer to use with alcohol, when there are no data upon which to base such a conclusion. Therefore, based, among other things, on the Panel's conclusions that these OTC internal analgesic/antipyretic active ingredients all have safety profiles similar to aspirin and should bear similar labeling, the agency is also proposing that OTC drug products containing carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate bear an alcohol warning.

C. OTC Internal Analgesic/Antipyretic Ingredients Switched From Prescription Status

After reviewing current data and information, and based on the Committees' recommendations, the agency is proposing to require an alcohol warning on all OTC drug products containing ibuprofen, ketoprofen, and naproxen sodium. Ibuprofen, ketoprofen, and naproxen sodium have been extensively marketed as prescription drugs at higher doses. Lower doses have been approved for OTC marketing through the new drug approval process. All OTC ketoprofen and naproxen sodium drug products are currently marketed with the following alcohol warning: "ALCOHOL WARNING [heading in bold face type]: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take [product name inserted] and other pain relievers."

Ibuprofen, ketoprofen, and naproxen sodium are derivatives of propionic acid and, as such, share common pharmacologic effects. As with aspirin, propionic acid derivatives produce adverse GI side effects, alter platelet function, and prolong bleeding time (Refs. 126 through 129). GI complications are the most common side effects of these drugs and can include problems such as irritation, nausea, vomiting, bleeding, hematemesis, and activation of peptic ulcer (Refs. 127 and 128).

Articles in the scientific literature suggest a definitive relationship between the ingestion of propionic acid derivatives at prescription doses and GI complications. In a review article, Greene and Winickoff (Ref. 130) discussed the effectiveness, side effects, and costs of aspirin and various prescription nonsteroidal anti-inflammatory drugs (NSAID's), including ibuprofen, ketoprofen, and naproxen sodium. The authors stated that NSAID's share the risks of causing

gastric ulcer, upper GI bleeding, and GI perforation, and that GI side effects occur in roughly 25 percent of NSAID users. The authors also cited studies (Ref. 130) that attribute a relative risk of 4.03 for gastric ulcer and 3.09 for upper GI bleeding in users of these drug products.

Langman et al. (Ref. 131) compared previous use of propionic acid derivatives and other prescription NSAID's in patients age 60 and older admitted to hospitals with bleeding from peptic ulcers to controls (in hospital and community) matched for sex and age. The investigators found that peptic ulcer bleeding was strongly associated with the use of propionic acid derivatives, aspirin, and other prescription NSAID's during the 3 months before admission and that the risk of bleeding increased as dosage increased. An analysis of the risk according to drug dose (low, medium, high) revealed an odds ratio of 2.5 (1.7 to 3.8, 95 percent confidence interval) when exposure was to lower doses of these drugs and increased to 4.5 (3.3 to 6.0, 95 percent confidence interval) when exposure was to moderate doses. The study defined low dose as: (1) Less than 1,200 mg/day (OTC maximum daily dose) for ibuprofen, (2) less than 500 mg/day for naproxen (OTC maximum daily dose 660 mg/day), and (3) less than 100 mg/day for ketoprofen (OTC maximum daily dose 75 mg).

The use of ibuprofen, ketoprofen, or naproxen sodium may also predispose an individual to bleeding from a preexisting ulcer or other upper GI lesion. Increased severity of GI irritation is related to increased dosage of drug. While less severe irritation could be expected at the lower OTC doses, there are no data to clarify the magnitude of the risk for individuals with preexisting GI lesions due to a history of heavy alcohol use or abuse. In fact, more recent information (Ref. 132) suggests that OTC doses of ibuprofen or naproxen sodium increase by three times the risk of GI bleeding and that this risk is increased when OTC drug products containing these ingredients are used by individuals who consume alcohol.

The Committees discussed the relationship between alcohol and toxicities associated with OTC internal analgesic/antipyretic drug products (Ref. 72) and concluded that the effect of alcohol and ibuprofen or naproxen sodium was at least additive and that heavy and/or chronic drinkers of alcohol are at an increased risk of severe gastritis and GI bleeding. The Committees recommended that an alcohol warning should be required on OTC drug products containing ibuprofen or naproxen sodium.

On July 14, 1995, the Committees discussed two NDA's for OTC ketoprofen products (Ref. 133). The Committees agreed that ketoprofen can be used safely and effectively OTC. However, the Committees voted unanimously that, based on past Committee discussions, products containing this new OTC ingredient should be required to have the same alcohol warning in their labeling as that required for naproxen sodium.

Based on the Committees' recommendations and information in the literature, the agency has concerns that the use of OTC internal analgesic/antipyretic drug products containing aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate by individuals with a history of heavy alcohol use or abuse may increase their risk of adverse GI effects, including serious GI bleeding. Therefore, the agency has determined that an alcohol warning is needed for OTC internal analgesic/antipyretic drug products containing these ingredients. The agency invites the submission of comments and additional data supporting the safe use of these ingredients by individuals with a history of heavy alcohol use or abuse.

VI. The Agency's Proposal

Current data and information indicate that individuals with a history of heavy alcohol use or abuse have an increased sensitivity to the hepatotoxic effects of acetaminophen. Currently available data on the use of OTC internal analgesic/antipyretic drug products containing aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, naproxen sodium, magnesium salicylate, and sodium salicylate raise the logical concern that these OTC products pose an increased risk of GI bleeding to these individuals (i.e., individuals with a history of heavy alcohol use or abuse). However, the available data are not sufficient to assess the magnitude of this risk. Therefore, the agency is proposing that all OTC internal analgesic/antipyretic drug products and any combination product containing one of these ingredients labeled for adult use, whether marketed pursuant to an OTC drug monograph or an NDA, bear an alcohol warning. This proposal follows the agency's Committees' (NDAC and ADAC) recommendations for such a warning on OTC internal analgesic/antipyretic drug products containing acetaminophen, aspirin, ibuprofen, ketoprofen, and naproxen sodium.

A comment submitted in response to NDAC's recommendation for an alcohol warning for OTC acetaminophen drug products advised that all OTC internal analgesic/antipyretic drug products should bear a common alcohol warning. The comment proposed the following warning: "Use of certain medicines with alcohol can cause adverse effects. Consult a physician for appropriate use of this or other pain relievers if every day you consume excessive amounts of alcohol." The comment suggested that this warning would avoid the potential consumer confusion that could result from a more-detailed, ingredient-specific warning. The comment mentioned the following advantages of this warning: (1) Its educational nature, i.e., the warning heightens consumer awareness of a possible interaction between alcohol and OTC internal analgesic/antipyretic drug products, and (2) it helps consumers to understand that they simply cannot switch to another OTC internal analgesic/antipyretic drug product to avoid this risk.

Under the new drug approval process, the agency has approved the marketing of OTC internal analgesic/antipyretic drug products containing ketoprofen and naproxen sodium. The following warning was included in the products' approved labeling (Refs. 134, 135, and 136): "ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take [product name] and other pain relievers." Subsequently, this warning was included in the approved labeling of an OTC extended release drug product containing acetaminophen (Ref. 136). In April of 1996, the agency requested the voluntary implementation of this alcohol warning on all OTC analgesic/antipyretic drug products (Ref. 138). This request was based on a lack of uniformity in the use of an alcohol warning and the resultant consumer confusion.

In the Federal Register of February 27, 1997 (62 FR 9024), the agency published a proposed rule to establish a standardized format for the labeling of OTC drugs. During the agency's evaluation of data relating to consumers' perception of label warnings it became clear that more specific information heightens the effectiveness of risk communication (Ref. 139). Therefore, the agency is concerned about the effectiveness of the general alcohol warning currently used and is proposing more specific alcohol warnings.

The warnings being proposed are similar to that suggested by the comment but contain more specific information. The warnings specify "3 or more" instead of the general term "excessive." The agency has included a specific number of drinks in the warnings to help consumers identify a level of alcohol consumption that may increase their risk from the use of OTC internal analgesic/antipyretic drug products. However, the agency acknowledges that the data are not sufficient to clearly identify a level of alcohol consumption that increases the risk of OTC internal analgesic/antipyretic drug use.

In the proposed warnings, the agency has included a level of alcohol consumption that is consistent with limitations on daily intake recommended by the AHA (Ref. 124) and by the Dietary Guidelines for Americans developed by the U.S. Departments of Agriculture and Health and Human Services (Ref. 125). The AHA recommends that men and women limit alcohol intake to 1 oz of alcohol per day and defines this amount as follows: (1) 2 oz of 100-proof whiskey, (2) 3 oz of 80-proof whiskey, (3) 8 oz of wine, or (4) 24 oz of beer. The Dietary Guidelines recommend no more than two drinks per day for men and one drink per day for women. The guidelines define one drink as follows: (1) 12 oz of regular beer, (2) 5 oz of wine, or (3) 1.5 oz of 80-proof distilled spirits. The agency believes that the number of drinks included in the proposed warnings are consistent with these recommendations. However, the agency invites comment on the proposed warnings specifying "3 or more alcoholic beverages daily."

In addition, the warnings being proposed include organ-specific information. When NDAC discussed a warning for acetaminophen, it recommended that product labeling refer specifically to possible damage to the liver. However, when the Committees considered the need for an alcohol warning for other OTC internal analgesic/antipyretic drug products (e.g., aspirin), they were unable to reach a consensus on whether the warning should be general or should specify bleeding or GI effects. Based on its recent experience with OTC consumer labeling, the agency has concluded that warnings containing more specific information are more effective. Therefore, the agency is proposing that OTC analgesic/antipyretic drug products containing acetaminophen, labeled for adult use, should bear the following warning: "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product name] or other pain relievers. [Product name] may increase your risk of liver damage." For OTC analgesic/antipyretic drug products containing other OTC active ingredients, i.e., aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, naproxen sodium, magnesium salicylate, and sodium salicylate, labeled for adult use, the agency is proposing the following warning: "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product name] or other pain relievers. [Product name] may increase your risk of stomach bleeding." The agency is proposing that OTC analgesic/antipyretic drug products containing acetaminophen in combination with any other OTC analgesic/antipyretic ingredient, labeled for adult use, should bear the following warning: "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product name] or other pain relievers. [Product name] may increase your risk of liver damage and stomach bleeding." However, the agency invites comment on the above organ-specific alcohol warnings.

VII. Voluntary Implementation

The agency acknowledges that these proposed alcohol warnings represent a significant change from the labeling required for OTC analgesic/antipyretic new drug products approved since naproxen sodium. Therefore, holders of approved applications for OTC internal analgesic/antipyretic drug products will not be required to implement the proposed warnings at this time. However, holders of approved applications for these drug products may implement the proposed warning without advance approval from FDA provided the warning includes at least the information in proposed § 201.322. A supplement must be submitted under § 314.70(c) (21 CFR 314.70(c)) in order to provide for the implementation of such labeling. The supplement and its mailing cover should be clearly marked: "Special Supplement—Changes Being Effected."

Voluntary compliance with these proposed warnings is subject to the possibility that FDA may change the wording of the statement, or not require the statement, as a result of comments filed in response to this proposal. Because FDA wishes to encourage the voluntary use of the proposed labeling statements, the agency advises that manufacturers will be given ample time after publication of a final rule to use up any labeling implemented in conformance with this proposal.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation) in any 1 year.

The agency believes that this proposed rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this proposed rule is to add a warning statement to the labeling of OTC drug products labeled for adult use containing internal analgesic/antipyretic active ingredients. The warning statement concerns the increased risk of adverse effects from the use of OTC analgesic/antipyretic drug products by individuals with a history of heavy alcohol use or abuse. Potential benefits include a reduced risk of adverse effects when these consumers use these products.

This proposed rule amends Subpart C—Labeling Requirements of Over-the-Counter Drugs of 21 CFR part 201 and will require relabeling for many OTC drug products containing internal analgesic/antipyretic active ingredients. The agency's Drug Listing System identifies approximately 600 manufacturers and distributors of 5,000 to 6,000 OTC analgesic/antipyretic drug products with an average of 3 stock keeping units (SKU) (individual products, packages, and sizes) per product. It is also likely that there are some additional marketers and products that are not currently included in the agency's system. Nonetheless, the agency estimates that there are a total of

600 manufacturers and distributors and an estimated 18,000 SKU's.

The agency has been informed that relabeling costs of this type generally average about $2,000 to $3,000 per SKU. Assuming that there are approximately 18,000 affected SKU's in the marketplace, total one-time costs of relabeling would be $36 to $48 million. However, the agency believes that the actual costs may be lower because the agency is allowing supplementary labeling (e.g., stick on labeling) to be used for products not undergoing a new labeling printing within the 6-month implementation period. The agency solicits comments on whether these estimates are accurate and whether there are other effects that the agency should consider (e.g., the cost to manufacturers due to the effect on sales because of the decreased use of these products; or the implications to patients who take these products prophylactically for conditions such as heart ailments).

The proposed rule would not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the proposed rule. The agency does not believe that there are any significant alternatives to the proposed rule that would adequately provide for the safe and effective use of OTC drug products containing analgesic/antipyretic active ingredients.

This proposed rule may have a significant economic impact on some small entities. The labeling of some of the affected products is prepared by private label manufacturers for small marketers. Census data provide aggregate industry statistics on the total number of manufacturers for Standardized Industrial Classification Code 2384 Pharmaceutical Preparations by establishment size, but do not distinguish between manfacturers of prescription and OTC drug products. According to the U.S. Small Business Administration (SBA) designations for this industry, however, over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms are small. (Because census size categories do not correspond to the SBA designation of 750 employees, these figures are based on 500 employees.)

An analysis of IMS America listings for manufacturers of OTC drug products found that from 46 to 69 percent of the 400 listed firms are small using the SBA definition of 750 employees. The agency's Drug Listing System indicates that about 600 marketers will need to relabel. Thus, the agency believes that many of the manufacturers affected by this proposal would be small. Further, some entities, such as those private label manufacturers that provide labeling for a number of the affected products may also incur a significant impact. However, the agency has allowed for a 6-month implementation period and the use of supplementary labeling (e.g., stick-on labeling) in an attempt to minimize the economic impact of the proposed regulation. The agency believes that these measures should help reduce relabeling costs for small entities.

The agency considered but rejected the following alternatives: (1) Voluntary relabeling, and (2) a longer implementation period. However, the agency does not consider either of these approaches acceptable because they do not ensure that consumers will have the most recent needed information for the safe and effective use of OTC drug products containing internal analgesic/antipyretic drug active ingredients.

This analysis shows that this proposed rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden of small entities. Nevertheless, some entities, especially those private label manufacturers that provide labeling for a number of the affected products, may incur significant impacts. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Act does not apply to the proposed rule because it would not result in an expenditure by State, local, or tribal governments, in the aggregate, or by the private sector, of $100 million in any 1 year.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers of drug products that contain OTC internal analgesic/antipyretic active ingredients. Comments regarding the impact of this rulemaking on these drug products should be accompanied by appropriate documentation. A period of 75 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirement proposed in this document is not subject to review by the Office of Management and Budget because it does not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed warning statement is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

X. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Public Comment

Interested persons may, on or before January 28, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Written comments on the agency's economic impact determination may be submitted on or before January 28, 1998. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Baeg, N., H. C. Bodenheimer, and K. Burchard, "Long-Term Sequelae of Acetaminophen-Associated Fulminant Hepatic Failure: Relevance of Early Histology," *American Journal of Gastroenterology*, 83:569–571, 1988.

2. Barker, J. D., D. J. deCarle, and S. Anuras, "Chronic Excessive Acetaminophen Use and Liver Damage," *Annals of Internal Medicine*, 87:299–301, 197[illegible]

3. Black, M. et al., "Late Presentation of Acetaminophen Hepatotoxicity," *Digestive Diseases and Sciences*, 27:370–374, 1982.

4. Dennison, H., J. Kaczynski, and S. Wallerstedt, "Paracetamol Medication and Alcohol Abuse: A Dangerous Combination for the Liver and the Kidney," *Scandinavian*

Journal of Gastroenterology, 22:701–704, 1987.

5. Emby, D. J., and B. N. Fraser, "Hepatotoxicity of Paracetamol Enhanced by Ingestion of Alcohol," *South African Medical Journal*, 51:208–209, 1977.

6. Fleckenstein, J. L., "Nyquil and Acute Hepatic Necrosis," *New England Journal of Medicine*, 1:48, 1985.

7. Floren, C., P. Thesleff, and Å. Nilsson, "Severe Liver Damage Caused by Therapeutic Doses of Acetaminophen," *Acta Medica Scandinavia*, 222:285–288, 1987.

8. Foust, R. T. et al., "Nyquil-Associated Liver Injury," *American Journal of Gastroenterology*, 84:422–425, 1989.

9. Gerber, M. A. et al., "Acetaminophen Associated Hepatic Injury—Report of Two Cases Showing Unusual Portal Tract Reactions," *Human Pathology*, 11:37–42, 1980.

10. Goldfinger, R. et al., "Concomitant Alcohol and Drug Abuse Enhancing Acetaminophen Toxicity," *American Journal of Gastroenterology*, 70:385–388, 1978.

11. Himmelstein, D. U., S. J. Woolhander, and R. D. Adler, "Elevated SGOT/SGPT Ratio in Alcoholic Patients with Acetaminophen Hepatotoxicity," *American Journal of Gastroenterology*, 79:718–720, 1984.

12. Johnson, M. W., P. A. Friedman, and W. E. Mitch, "Alcoholism, Nonprescription Drugs and Hepatotoxicity–The Risk From Unknown Acetaminophen Ingestion," *American Journal of Gastroenterology*, 76:530–532, 1981.

13. Kartsonis, A., K. R. Reddy, and E. R. Schiff, "Alcohol, Acetaminophen, and Hepatic Necrosis," *Annals of Internal Medicine*, 105:138–139, 1986.

14. Kaysen, G. A. et al., "Combined Hepatic and Renal Injury in Alcoholics During Therapeutic Use of Acetaminophen," *Archives of Internal Medicine*, 145:2019–2023, 1985.

15. Kromhout, J. P., J. D. Holtzman, and C. J. McClain, "Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Gastroenterology*, 76:1288, 1980.

16. LaBreque, D. R., and F. A. Mitros, "Increased Hepatotoxicity of Acetaminophen in the Alcoholic," *Gastroenterology*, 78:1310, 1980.

17. Leist, M. H., L. E. Gluskin, and J. A. Payne, "Enhanced Toxicity of Acetaminophen in Alcoholics: Report of Three Cases," *Journal of Clinical Gastroenterology*, 7:55–59, 1985.

18. Lesser, P. B., M. M. Vietti, and W. D. Clark, "Lethal Enhancement of Therapeutic Doses of Acetaminophen by Alcohol," *Digestive Diseases and Sciences*, 31:103–105, 1986.

19. Levinson, M., "Ulcer, Back Pain, and Jaundice in an Alcoholic," *Hospital Practice*, Oct:48N and 48S, 1983.

20. Licht, H., L. B. Seeff, and H. J. Zimmerman, "Apparent Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Annals of Internal Medicine*, 12:511, 19[illegible]

21. Litovitz, T. L. et al., "1987 Annual Report of the American Association of Poison Control Centers National Data Collection System," *American Journal of Emergency Medicine*, 6:479–515, 1988.

22. McClain, C. J. et al., "Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Journal of the American Medical Association*, 244:251–253, 1980.

23. McClain, C. J. et al., "Clinical Features of Acetaminophen Toxicity," *Journal of Clinical Gastroenterology*, 10:76–80, 1988.

24. O'Dell, J. R., R. K. Zetterman, and D. A. Burnett, "Centrilobular Hepatic Fibrosis Following Acetaminophen-Induced Hepatic Necrosis in an Alcoholic," *Journal of the American Medical Association*, 255:2632–2633, 1986.

25. Pezzano, M. et al., "Hepatic and Renal Toxicity of Paracetamol in Chronic Alcoholic Subjects," *Press Médicale*, 17:21–24, 1988.

26. Seeff, L. B. et al., "Acetaminophen Hepatotoxicity in Alcoholics," *Annals of Internal Medicine*, 104:399–404, 1986.

27. Villeneuve, J. P. et al., "Pharmacokinetics and Metabolism of Acetaminophen in Normal, Alcoholic, and Cirrhotic Subjects," *Gastroenterology and Clinical Biology*, 7:898–902, 1983.

28. Dietz, A. J. et al., "Effects of Alcoholism on Acetaminophen Pharmacokinetics in Man," *Journal of Clinical Pharmacology*, 24:205–208, 1984.

29. Wójcicki, J. et al., "The Effect of a Single Dose of Ethanol on the Pharmacokinetics of Paracetamol," *Polish Journal of Pharmacology and Pharmacy*," *30:749–753, 1978.*

30. Peterson, F. J. et al., "Ethanol Induction of Acetaminophen Toxicity and Metabolism," *Life Sciences*, 27:1705–1711, 1980.

31. Teschke, R., G. Stutz, and G. Strohmeyer, "Increased Paracetamol-Induced Hepatotoxicity After Chronic Alcohol Consumption," *Biochemical and Biophysical Research Communications*, 91:368–374, 1979.

32. Guerri, C., and S. Grisolia, "Decreased Glutathione in Rats Due to Chronic Intake of Ethanol," *Federation Proceedings*, 36:1541, 1978.

33. Pessayre, D. et al., "Effect of Fasting on Metabolite-Mediated Hepatotoxicity in the Rat," *Gastroenterology*, 77:264–271, 1979.

34. McLean, A. E. M., and P. A. Day, "The Effect of Diet on the Toxicity of Paracetamol and the Safety of Paracetamol-Methionine Mixtures," *Biochemical Pharmacology*, 24:37–42, 1975.

35. Mitchell, J. R. et al., "Acetaminophen-Induced Hepatic Necrosis IV Protective Role of Glutathione," *Journal of Pharmacology and Experimental Therapeutics*, 187:211–217, 1973.

36. Wright, N., and L. F. Prescott, "Potentiation by Previous Drug Therapy of Hepatotoxicity Following Paracetamol Overdosage," *Scottish Medical Journal*, 18:56–58, 1973.

37. Strubelt, O., F. Obermeier, and C. P. Siegers, "The Influence of Ethanol Pretreatment on the Effects of Nine Hepatotoxic Agents," *Acta Pharmacologica and Toxicologica*, 43:211–218, 1978.

38. Sato, C., Y. Matsuda, and C. S. Lieber, "Increased Hepatotoxicity of Acetaminophen after Chronic Ethanol Consumption in the Rat," *Gastroenterology*, 80:140–148, 1981.

39. Sato, C., M. Nakano, and C. S. Lieber, "Prevention of Acetaminophen-Induced Hepatotoxicity by Acute Ethanol Administration in the Rat: Comparison with Carbon Tetrachloride-Induced Hepatotoxicity," *Journal of Pharmacology and Experimental Therapeutics*, 218:805–810, 1981.

40. Sato, C., and C. S. Lieber, "Mechanism of the Preventive Effect of Ethanol on Acetaminophen-Induced Hepatotoxicity," *Journal of Pharmacology and Experimental Therapeutics*, 218:811–815, 1981.

41. Rumack, B. H. et al., "Acetaminophen Overdose," *Archives of Internal Medicine*, 141:380–385, 1981.

42. Lieber, C. S, "Interaction of Alcohol and Drugs," *Practical Gastroenterology*, 7:23–24, 29–30, and 48, 1983.

43. Altomare, E. et al., "Interaction of Ethanol with Acetaminophen Metabolism in the Baboon," *Biochemical Pharmacology*, 31:2207–2212, 1984.

44. Banda, P. W., and B. D. Quart, "The Effect of Mild Alcohol Consumption on the Metabolism of Acetaminophen in Man," *Research Communications in Chemical Pathology and Pharmacology*, 38:57–70, 1982.

45. Strubelt, O., "Alcohol Potentiation of Liver Injury," *Fundamental and Applied Toxicology*, 4:144–151, 1984.

46. Rosen, G. M. et al., "Acetaminophen Hepatotoxicity an Alternative Mechanism," *Biochemical Pharmacology*, 32:2053–2059, 1983.

47. *The Encyclopedia of Alcoholism*, Facts on File Publication, New York, 1982, s.v. "alcoholism" and "consumption".

48. *United States Pharmacopeial Dispensing Information—1993: Vol. I Drug Information for the Health Care Professional*, 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 3–4.

49. *United States Pharmacopeial Dispensing Information—1993: Vol. II Advice for the Patient Drug Information in Lay Language*, 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 3.

50. Black, M., "Acetaminophen, Alcohol, and the Liver," *Philadelphia Medicine*, 82:230–237, 1986.

51. Davis, A. M. et al., "Severe Hepatic Damage After Acetaminophen Use in Psittacosis," *American Journal of Medicine*, 74:349–352, 1983.

52. Kumar, S., and D. Rex, "Failure of Physicians to Recognize Acetaminophen Hepatotoxicity in Chronic Alcoholics," *Archives of Internal Medicine*, 151:1189–1191, 1991.

53. Wooton, F., and W. Lee, "Acetaminophen Hepatotoxicity in the Alcoholic," *Southern Medical Journal*, 83:1047–1049, 1990.

54. Bray, G. et al., "The Effect of Chronic Alcohol Intake on Prognosis and Outcome in Paracetamol Overdose," *Human Experimental Toxicology*, 10:435–438, 1991.

55. Girre, C. et al., "Increased Metabolism of Acetaminophen in Chronically Alcoholic Patients," *Alcoholism Clinical and Experimental Research*, 17:170–173, 1993.

56. Comment No. C150, Docket No. 77N–0094, Dockets Management Branch.

57. Bell, H., H. Schonsby, and N. Raknerud, "Severe Liver Damage After Therapeutic Doses of Paracetamol," *Journal of the Norwegian Medical Association*, 107:1037–1040, 1987.

58. Bidault, I. et al., "Do Cases of Hepatitis Due to the Subacute Toxicity of Acetaminophen Exist?," *Therapy*, 42:387–388, 1987.

59. Erickson, R. A., and B. A. Runyon, "Acetaminophen Hepatotoxicity Associated with Alcoholic Pancreatitis," *Archives of Internal Medicine*, 144:1509, 1513, 1984.

60. Luquel, L. et al., "Acute Hepato-Nephritis in an Alcoholic Following a Therapeutic Dose of Acetaminophen," *La Presse Medicale*, 17:1318, 1988.

61. Stolt, C., and S. Johnsen, "A Therapeutic Intake of Paracetamol Causes Acute Renal Insufficiency and Liver Damage," *Larkartidningen*, 81:1313, 1984.

62. Vilstrup, V., N. C. Henningsen, and L. F. Hansen, "Liver Damage After Paracetamol," *Ugeskrift for Laeger*, 139:831–834, 1977.

63. Critchley, J. et al., "Is There a Place for Cimetidine or Ethanol in the Treatment of Paracetamol Poisoning," *Lancet*, 1:1375–1376, 1983.

64. Critchley, J. et al., "Paracetamol Metabolism in Heavy Drinkers," *British Journal of Clinical Pharmacology*, 13:276P–277P, 1982.

65. Lauterburg, B. H., and M. E. Velez, "Glutathione Deficiency in Alcoholics: Risk Factor for Paracetamol Hepatotoxicity," *Gut*, 29:1153–1157, 1988.

66. Farrell, G. C., W. G. E. Cooksley, and L. W. Powell, "Drug Metabolism in Liver Disease: Activity of Hepatic Microsomal Metabolizing Enzymes," *Clinical Pharmacology and Therapeutics*, 26:483–492, 1979.

67. Gabrielle, L. et al., "Determination of Human Liver Cytochrome P450 by a Micromethod Using Electron Paramagnetic Resonance. Study of 141 Liver Biopsies," *Gastroenterology and Clinical Biology*, 1:775–782, 1977.

68. Schoene, B. et al., "Determination of Drug Metabolizing Enzymes in Needle Biopsies of Human Liver," *European Journal of Clinical Pharmacology*, 4:65–73, 1972.

69. Data and information provided for June 28 and 29, 1993, meeting of the FDA Nonprescription Drugs Advisory Committee, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

70. Summary minutes of the June 28 and 29, 1993, meeting of the FDA Nonprescription Drugs Advisory Committee, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

71. Data and information provided for the September 8, 1993, joint meeting of the FDA Nonprescription Drugs and Arthritis Drugs Advisory Committees, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

72. Summary minutes of the September 8, 1993, joint meeting of the FDA Nonprescription Drugs and Arthritis Drugs Advisory Committees, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

73. Comment No. C193, Docket No. 77N–0094, Dockets Management Branch.

74. "A Prospective Observational Study of Adult Patients with Upper Gastrointestinal Disease with Hemorrhage and a History of Alcohol and Nonsteroidal Anti-inflammatory Drug Ingestion with Primary Emphasis on Aspirin, Over-the-Counter Ibuprofen, and Naproxen," draft of an unpublished paper included in Comment No. C188, Docket No. 77N–0094, Dockets Management Branch.

75. "A Retrospective Review of Serious Acute Upper Gastrointestinal Bleeding Associated with the Prior Use of Alcohol and Nonsteroidal Anti-inflammatory Drugs," draft of an unpublished paper included in Comment No. C188, Docket No. 77N–0094, Dockets Management Branch.

76. "Summary of Prospective Case Control Study from SUNY Health Science Center on the Epidemiology of Nonsteroidal Anti-inflammatory Drug Use in Patients with Upper Gastrointestinal Bleeding," draft of an unpublished paper included in Comment No. C188, Docket No. 77N–0094, Dockets Management Branch.

77. Kelly, J., D. Kaufman, and S. Shapiro, "The Risk of Major Upper Gastrointestinal Bleeding Among Users of Aspirin, Ibuprofen, Naproxen, at Various Levels of Alcohol Consumption," draft of an unpublished paper included in Comment No. C188, Docket No. 77N–0094, Dockets Management Branch.

78. Strom, B., "Gastrointestinal Bleeding Associated with Over-the-Counter Use of Ibuprofen and Aspirin," draft of an unpublished paper included in Comment No. C188, Docket No. 77N–0094, Dockets Management Branch.

79. Henry, D., A. Dobson, and C. Turner, "Variability in the Risk of Major Gastrointestinal Complications from Nonaspirin Nonsteroidal Anti-inflammatory Drugs," *Gastroenterology*, 105:1078–1088, 1993.

80. Comments No. C198, C199, and C200, Docket No. 77N–0094, Dockets Management Branch.

81. Black, M., "Acetaminophen Hepatotoxicity," *Annual Reviews in Medicine*, 35:577–593, 1984.

82. Proudfoot, A. T., and N. Wright, "Acute Paracetamol Poisoning," *British Medical Journal*, 3:557–558, 1970.

83. Arthurs, Y., and J. F. Fielding, "Paracetamol and Chronic Liver Disease," *Journal of the Irish Medical Association*, 73:273–274, 1980.

84. Bonkowsky, H. L., "Chronic Hepatic Inflammation and Fibrosis Due to Low Doses of Paracetamol," *Lancet*, 1:1016–1018, 1978.

85. Bravo-Fernández, E. F. et al., "Hepatotoxicity After Prolonged Use of Acetaminophen: Case Report," *Boletin-Asociacion Medica de Puerto Rico*, 80:417–419, 1988.

86. Edwards, R., and J. Oliphant, "Paracetamol Toxicity in Chronic Alcohol Abusers—A Plea for Greater Consumer Awareness," *New Zealand Medical Journal*, 105:174–175, 1992.

87. Eriksson, L. S. et al., "Hepatotoxicity Due to Repeated Intake of Low Doses of Paracetamol," *Journal of Internal Medicine*, 231:567–570, 1992.

88. Itoh, S. et al., "Cirrhosis Following 12 Years of Treatment with Acetaminophen," *Hepato-Gastroenterology*, 30:58, 1983.

89. Olsson, R., "Increased Hepatic Sensitivity to Paracetamol," *Lancet*, 2:152–153, 1978.

90. Pirotte, J. H., "Apparent Potentiation by Phenobarbital of Hepatotoxicity from Small Doses of Acetaminophen," *Annals of Internal Medicine*, 101:403, 1984.

91. Rosenberg, D. M. et al., "Acetaminophen and Hepatic Dysfunction in Infectious Mononucleosis," *Southern Medical Journal*, 70:660–661, 1977.

92. Ware, A. J. et al., "Acetaminophen and the Liver," *Annals of Internal Medicine*, 88:267–268, 1978.

93. Whitcomb, D. C., and G. D. Block, "Association of Acetaminophen Hepatotoxicity with Fasting and Ethanol Use," *Journal of the American Medical Association*, 272:1845–1850, 1994.

94. Letter from P. A. Malone, Stein, Mitchell, and Mezines, to D. A. Kessler, FDA, dated March 11, 1996, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

95. Zimmerman, H. J., and W. C. Maddrey, "Acetaminophen (Paracetamol) Hepatotoxicity with Regular Intake of Alcohol: Analysis of Instances of Therapeutic Misadventure," *Hepatology*, 22:767–773, 1995.

96. Lee, W. M., "Drug Induced Hepatotoxicity," *New England Journal of Medicine*, 333:1118–1127, 1995.

97. Tarnawski, A. et al., "Alcohol Injury to the Normal Gastric Mucosa: Endoscopic, Histologic, and Functional Assessment," *Clinical Investigations in Medicine*, 10:259–263, 1987.

98. Soll, A. H., "Gastritis," in *Cecil Textbook of Medicine*, 19th ed., edited by J. B. Wyngaarden, L. H. Smith, and J. C. Bennett, W. B. Saunders Co., Philadelphia, pp. 649–650, 1992.

99. Domschke, S., and W. Domschke, "Gastrointestinal Damage Due to Drugs, Alcohol and Smoking," in *Clinics in Gastroenterology*, W. B. Saunders Co., London, pp. 419–424, 1984.

100. MacMath, T. L., "Alcohol and Gastrointestinal Bleeding," *Emergency Medicine Clinics of North America*, 8:859–872, 1990.

101. Steering Committee of the Physicians' Health Study Research Group, "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine*, 321:129–135, 1989.

102. Peto, R. et al., "Randomized Trial of Prophylactic Daily Aspirin in British Male Doctors," *British Medical Journal*, 296:313–316, 1988.

103. Juul-Möller, S. et al., "Double-Blind Trial of Aspirin in Primary Prevention of Myocardial Infarction in Patients with Stable Chronic Angina Pectoris," *Lancet*, 340:1421–1425, 1992.

104. Elwood, P. C., and P. M. Sweetnam, "Aspirin and Secondary Mortality After Myocardial Infarction," *Lancet*, II:1313–1315, 1979.

105. Fields W. S., et al., "Controlled Trial of Aspirin in Cerebral Ischemia," *Stroke*, 8:301–316, 1977.

106. UK–TIA Study Group, "United Kingdom Transient Ischaemic Attack (UK-TIA) Aspirin Trial: Interim Results," *British Medical Journal*, 296:316–320, 1988.

107. Bousser, M. G. et al., "'AICLA' Controlled Trial of Aspirin and Dipyridamole

in the Secondary Prevention of Athero-Thrombotic Cerebral Ischemia," *Stroke*, 14:5–14, 1983.

108. A Swedish Cooperative Study, "High-Dose Acetylsalicylic Acid After Cerebral Infarction," *Stroke*, 18:325–334, 1987.

109. Fields, W. S. et al., "Controlled Trial of Aspirin in Cerebral Ischemia. Part II: Surgical Group," *Stroke*, 9:309–318, 1978.

110. The SALT Collaborative Group, "Swedish Aspirin Low-dose Trial (SALT) of 75 mg Aspirin as Secondary Prophylaxis After Cerebrovascular Ischaemic Events," *Lancet*, 338:1345–1349, 1991.

111. The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," *Journal of Chronic Disease*, 29:625–642, 1976.

112. Aspirin Myocardial Infarction Study Research Group, "A Randomized, Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction," *Journal of the American Medical Association*," 243:661–669, 1980.

113. The Persantine-Aspirin Reinfarction Study Research Group, "Persantine and Aspirin in Coronary Heart Disease," *Circulation*, 62:449–461, 1980.

114. Breddin, K. et al., "The German-Austrian Aspirin Trial: A Comparison of Acetylsalicylic Acid, Placebo and Phenprocoumon in Secondary Prevention of Myocardial Infarction," *Circulation*, 62 (Suppl V):63–72, 1980.

115. Lewis, H. K. et al., "Protective Effects of Aspirin Against Acute Myocardial Infarction and Death in Men with Unstable Angina," *New England Journal of Medicine*, 309:396–403, 1983.

116. Petersen, P. et al., "Placebo-Controlled, Randomized Trial of Warfarin and Aspirin for Prevention of Thromboembolic Complications in Chronic Atrial Fibrillation," *Lancet*, 1:175–179, 1989.

117. Sanz, G. et al., "Prevention of Early Aortocoronary Bypass Occlusion by Low-Dose Aspirin and Dipyridamole," *Circulation*, 82:765–773, 1990.

118. Gavaghan, T. et al., "Immediate Postoperative Aspirin Improves Vein Graft Patency Early and Late After Coronary Artery Bypass Graft Surgery," *Circulation*, 83:1526–1533, 1991.

119. Elwood, P. C. et al., "A Randomized Controlled Trial of Acetyl-Salicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction," *British Medical Journal*, 1:436–440, 1974.

120. Slattery, C. P. et al., "Risks of Gastrointestinal Bleeding During Secondary Prevention of Vascular Events with Aspirin—Analysis of Gastrointestinal Bleeding During the UK-TIA Trial," *Gut*, 37:509–511, 1995.

121. Marmot, M., and E. Brunner, "Alcohol and Cardiovascular Disease: The Status of the U-Shaped Curve," *British Medical Journal*, 7:565–568, 1991.

122. National Institutes of Health, Eighth Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health and Human Services, U.S. Department of Health and Human Services, National Institutes of Health, and National Institute on Alcohol Abuse and Alcoholism, NIH Publication No. 94-3699, 1994.

123. Pohorecky, L. A., "Interaction of Alcohol and Stress at the Cardiovascular Level," *Alcohol*, 7:537–546, 1990.

124. American Heart Association, "Alcohol," in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

125. Nutrition and Your Health: Dietary Guidelines for Americans, U.S. Department of Agriculture and U.S. Department of Health and Human Services, Home and Garden Bulletin No. 232, U.S. Department of Agriculture.

126. Gilman, A. G. et al., editors, *The Pharmacological Basis of Therapeutics*, 8th ed., McGraw-Hill, New York, pp. 643 and 664–668, 1990.

127. Dukes, M. N. G., editor, *Meyler's Side Effects of Drugs*, 12th ed., Elsevier, Amsterdam, pp. 201–205, 1992.

128. Gennaro, A. R. et al., editors, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Co., Easton, PA, pp. 1112, 1117, and 1118, 1990.

129. Van Tyle, K. W., "Internal Analgesic Products," in *Handbook of Nonprescription Drugs*, 10th ed., American Pharmaceutical Association, Washington, pp. 59 and 62, 1993.

130. Greene, J. M., and R. N. Winickoff, "Cost-Conscious Prescribing of Nonsteroidal Anti-Inflammatory Drugs for Adults with Arthritis," *Archives of Internal Medicine*, 152:1995–2002, 1992.

131. Langman, M. J. S. et al., "Risks of Bleeding Peptic Ulcer Associated with Individual Non-Steroidal Anti-Inflammatory Drugs," *The Lancet*, 343:1075–1078, 1994.

132. Peura, D. et al., "ACG Bleeding Registry (BR): Preliminary Findings," abstract of an unpublished study in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

133. Draft Summary Minutes of the Nonprescription Drugs Advisory Committee and the Arthritis Advisory Committee, July 14, 1995, in OTC. Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

134. "Approved Labeling, Aleve," NDA 20–204, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

135. "Approved Labeling, Orudis," NDA 20–429, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

136. "Approved Labeling, Actron," NDA 20–499, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

137. "Approved Labeling, Tylenol Extended Relief Caplets," NDA 19–872, in OTC Vol. 03AWNPR, Docket No. 77N–094W, Dockets Management Branch.

138. Letter from D. L. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET126, Docket No. 77N–0094, Dockets Management Branch.

139. Laughery, K. et al., "Explicitness of Consequence Information in Warnings," *Safety Science*, 16:597–613, 1993.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. New § 201.322 is added to subpart G to read as follows:

§ 201.322 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required alcohol warning.

(a) People who regularly consume large quantities of alcohol have an increased risk of adverse effects (possible liver damage or gastrointestinal bleeding) when they use over-the-counter (OTC) drug products containing internal analgesic/antipyretic active ingredients. FDA concludes that the labeling of OTC drug products containing internal analgesic/antipyretic active ingredients should advise consumers with a history of heavy alcohol use or abuse to consult a physician about the use of these products. Accordingly, any OTC drug product, labeled for adult use, containing internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) shall bear an alcohol warning statement in its labeling as follows:

(1) *Acetaminophen.* "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product name] or other pain relievers. [Product name] may increase your risk of liver damage."

(2) *Aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.* "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product name] or other pain relievers. [Product name] may increase your risk of stomach bleeding."

(3) *Combinations of acetaminophen with other analgesic/antipyretic active ingredients listed in § 201.322(a)(2).* "Alcohol Warning" [heading in boldface type]: "If you drink 3 or more alcoholic beverages daily, ask your doctor whether you should take [insert product

name] or other pain relievers. [Product name] may increase your risk of liver damage and stomach bleeding."

(b) *Requirements to supplement approved application.* Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph (a) of this section must submit supplements under § 314.70(c) of this chapter to include the required warning in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes at least the information included in paragraph (a) of this section.

(c) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after (date 6 months after date of publication of the final rule in the Federal Register), is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is subject to regulatory action.

Dated: August 20, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97-30035 Filed 11-13-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

25 CFR Part 11

RIN 1076-AD76

Law and Order on Indian Reservations; Correction

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Correction to proposed regulations.

SUMMARY: This document contains corrections to the proposed regulations which were published Friday, July 5, 1996 (61 FR 35158) and corrections to the proposed regulations which were published Wednesday, February 26, 1997 (62 FR 8665). The proposed rule amends regulations governing Courts of Indian Offenses.

DATES: Comments must be received on or before December 15, 1997.

ADDRESSES: Comments are to be mailed to Bettie Rushing, Office of Tribal Services, Bureau of Indian Affairs, 1849 C Street, NW, MS 4641-MIB, Washington, DC 20240; or, hand delivered to Room 4641 at the same address.

FOR FURTHER INFORMATION CONTACT: Bettie Rushing, Bureau of Indian Affairs (202) 208-4400.

SUPPLEMENTARY INFORMATION:

Background

The proposed rule that is the subject of these corrections supersedes 25 CFR 11.100(a) and affects those tribes that have exercised their inherent sovereignty by removing the names of those tribes from the list of Courts of Indian Offenses.

The Assistant Secretary-Indian Affairs, or her designee, has received law and order code adopted by the Confederated Tribes of the Goshute Reservation of Nevada in accordance with their constitutions and by-laws and approved by the appropriate bureau official. The Assistant Secretary-Indian Affairs recognizes that this court was established in accordance with the tribe's constitutions and by-laws. Also, the list of Courts of Indian Offenses has been corrected to include tribes inadvertently omitted from the correction and to reflect the decision of the Court in *Fletcher* v. *United States*, No. 95-5208 (10th Cir. Dec. June 10, 1997, reh. den. Aug. 18, 1997).

Inclusion in § 11.100, *Where are Courts of Indian Offenses established?*, does not defeat the inherent sovereignty of a tribe to establish tribal courts and exercise jurisdiction under tribal law. *Tillett* v. *Lujan*, 931 F.2d 636, 640 (10th Cir. 1991) (CFR courts "retain some characteristics of an agency of the federal government" but they "also function as tribal courts"); *Combrink* v. *Allen*, 20 Indian L. Rep. 6029, 6030 (Ct. Ind. App., Tonkawa, Mar. 5, 1993) (CFR court is a "federally administered tribal court"); *Ponca Tribal Election Board* v. *Snake*, 17 Indian L. Rep. 6085, 6088 (Ct. Ind. App., Ponca, Nov. 10, 1988) ("The Courts of Indian Offenses act as tribal courts since they are exercising the sovereign authority of the tribe for which the court sits."). Such exercise of inherent sovereignty and the establishment of tribal courts shall comply with the requirements in 25 CFR 11.100(c).

Need for Correction

As published, the proposed rule and the correction to the proposed rule contain errors which may prove to be misleading and are in need of clarification.

Correction of Publication

Accordingly, the publication on July 5, 1996 (61 FR 35158), of the proposed regulations, which were the subject of FR Doc. 96-16039, and the publication of February 26, 1997 (62 FR 8664), corrections to the proposed regulations, which were the subject of FR Doc. 97-4686, are corrected as follows:

§ 11.100 [Corrected]

In the Federal Register published July 5, 1996 on page 35159, and corrected on February 26, 1997 on 1997 on page 8665, in § 11.100, paragraph (a) is, corrected to read as follows:

§ 11.100 Where are Courts of Indian Offenses established?

(a) Unless indicated otherwise in this part, the regulations in this part apply to the Indian country (as defined in 18 U.S.C. 1151) occupied by the tribes listed below:

(1) Red Lake Band of Chippewa Indians (Minnesota).

(2) Te-Moak Band of Western Shoshone Indians (Nevada).

(3) Yomba Shoshone Tribe (Nevada).

(4) Kootenai Tribe (Idaho).

(5) Shoalwater Bay Tribe (Washington).

(6) Eastern Band of Cherokee Indians (North Carolina).

(7) Ute Mountain Ute Tribe (Colorado).

(8) Quechan Indian Tribe (Arizona) (except resident members).

(9) Hoopa Valley Tribe, Yurok Tribe, and Coast Indian Community of California (California jurisdiction limited to special fishing regulations).

(10) Louisiana Area (includes Coushatta and other tribes located in the State of Louisiana which occupy Indian country and which accept the application of this part): *Provided*, that this part shall not apply to any Louisiana tribe other than the Coushatta Tribe until notice of such application has been published in the Federal Register.

(11) For the following tribes located in the former Oklahoma Territory (Oklahoma):

(i) Absentee Shawnee Tribe of Indians of Oklahoma.

(ii) Apache Tribe of Oklahoma.

(iii) Caddo Tribe of Oklahoma.

(iv) Cheyenne-Arapaho Tribe of Oklahoma.

(v) Citizen Band of Potawatomi Indians of Oklahoma.

(vi) Comanche Tribe of Oklahoma (Except Comanche Children's Court).

(vii) Delaware Tribe of Western Oklahoma.

(viii) Fort Sill Apache Tribe of Oklahoma.

(ix) Iowa Tribe of Oklahoma.

(x) Kaw Tribe of Oklahoma.

(xi) Kickapoo Tribe of Oklahoma.

(xii) Kiowa Tribe of Oklahoma.

(xiii) Otoe-Missouria Tribe of Oklahoma.